A RANDOMIZED CONTROLLED UNMASKED TRIAL COMPARING SAFETY AND EFFICACY OF ORAL MISOPROSTOL WITH INTRAVENOUS OXYTOCIN FOR INDUCTION IN PRELABOUR RUPTURE OF MEMBRANES AT TERM

Dissertation submitted to the

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By

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DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

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CERTIFICATE

This is to certify that the dissertation entitled **A randomized controlled unmasked trial comparing safety and efficacy of oral misoprostol with intravenous oxytocin for induction in prelabour rupture of membranes at term** is original work of Dr Shiny Nirupama Boddu under my guidance towards MS Branch II (Obstetrics and Gynaecology) Degree examination of Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2017.

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DECLARATION

I, SHINY NIRUPAMA, do hereby declare that the dissertation titled "**a randomized controlled unmasked trial comparing safety and efficacy of oral misoprostol with intravenous oxytocin for induction in prelabour rupture of membranes at term"** is a genuine record of research done by me under the supervision and guidance of Dr. Jiji .E.Mathews , Professor and Head of Unit , Department of Obstetrics and Gynaecology, Christian Medical College, Vellore and has not previously formed the basis of award of any degree, diploma, fellowship or other similar title of any university or institution.

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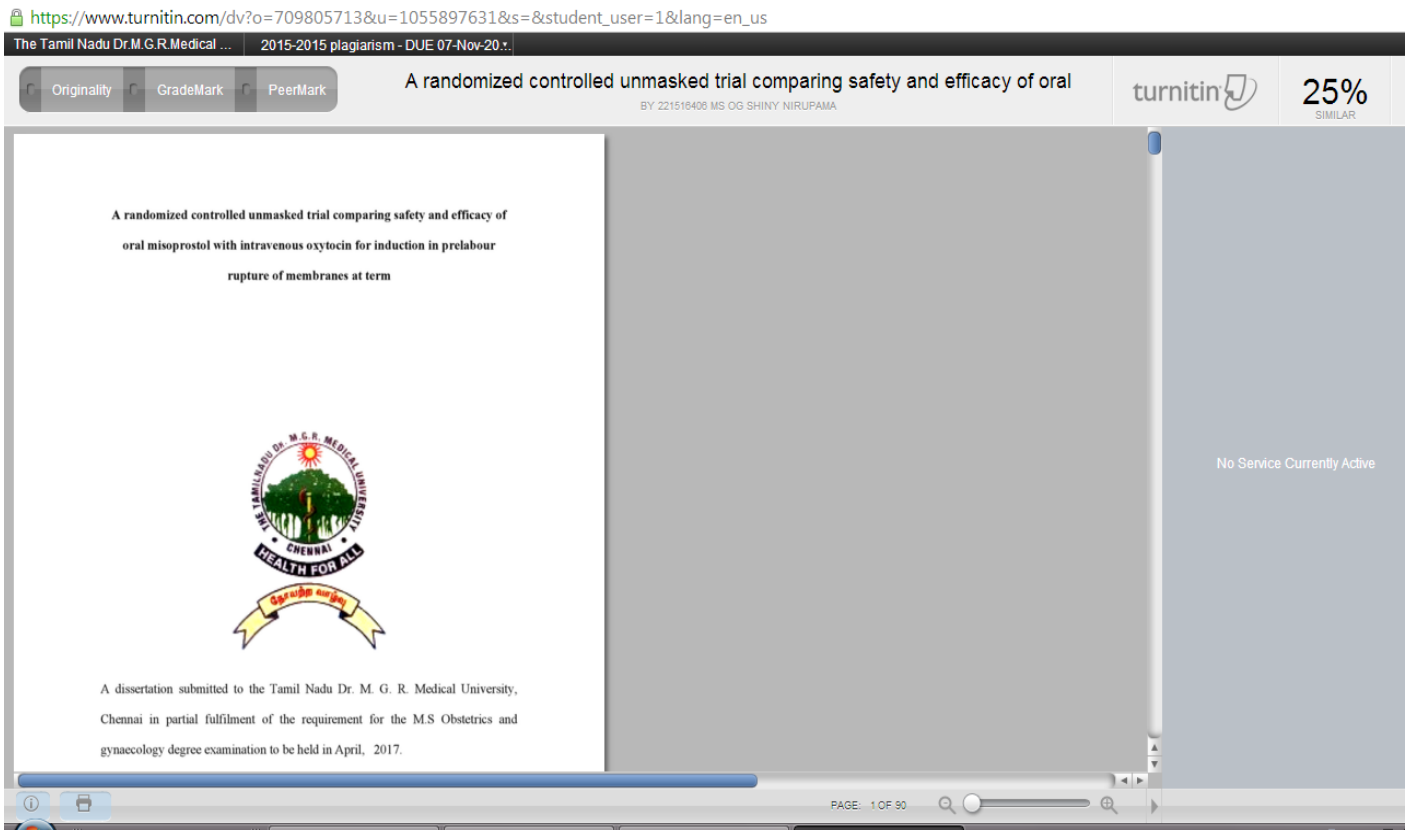
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INTRODUCTION

The terms Prelabour rupture of membranes/premature rupture of membranes (PROM) is defined as rupture of membranes prior to the onset of labour at or beyond 37 weeks of gestation. Incidence of PROM is 8 percent at term. 60% of these begin labour spontaneously within 24hrs, and over 95% within 72hours if labour is not induced(1).

However immediate induction is associated with decreased infectious maternal morbidity and neonatal ICU admission without increasing the rate of caesarean

deliveries and operative vaginal deliveries(2). Meta-analysis of randomised trials have shown a definite benefit from initial use of prostaglandins in women with PROM including those with unfavourable cervix.

Different regimens exist about the ideal method of active management. Options include mechanical method, intravenous oxytocin, vaginal prostaglandin E2, Vaginal misoprostol, sublingual and oral misoprostol. Titration of intravenous, oxytocin is the most common method used, but this is associated with restriction of patients ambulation , and continuous assessment is required for dosage control(3).

Oral misoprostol is inexpensive, easily available and stable at room temperature and has greater acceptability among women. Research done in our institution on term induction without the rupture of membranes has shown that women in the group that received oral misoprostol were more likely to develop uterine contractions without oxytocin than the women given vaginal misoprostol. Thus, due to ease in administration, especially in women with prelabour rupture of membranes we decided to use oral misoprostol.

A study done by Hussain et al (4)where 100micrograms of oral misoprostol was compared with intravenous oxytocin for labour induction in women with PROM at term and showed that oral misoprostol has shorter time interval between induction to delivery.

However contractile abnormalities like tachysystole and uterine hyper stimulation were higher in misoprostol group and they concluded that further studies were necessary to find the dose that is safe and effective. The aim of this randomised controlled trial is to compare safety and efficacy of 50microgram oral misoprostol with intravenous oxytocin in prelabour rupture of membranes at term.

AIM

The aim of this randomised controlled trial is to compare the safety and efficacy of oral misoprostol with intravenous oxytocin for induction in prelabour rupture of membranes at term.

PRIMARY OUTCOME

- Duration between induction and delivery.
- Vaginal delivery achieved within 24hours
- Caesarean section

SECONDARY OUTCOMES

Secondary outcomes relate to measures of effectiveness, complications and satisfaction.

1. Measures of effectiveness

- Need for oxytocin augmentation.

2. Complications

- Serious neonatal morbidity or perinatal death (e.g. sepsis, seizures, birth asphyxia, neonatal encephalopathy)
- Serious maternal morbidity or death (e.g. sepsis, admission to ICU, septicaemia, traumatic post-partum haemorrhage.
- Fever, chorioamnionitis, endometritis
- Apgar score less than seven at five minutes.
- Neonatal intensive care unit admission.
- Maternal nausea
- Maternal diarrhoea
- Other maternal side effects.
- Post-partum haemorrhage > 500ml of blood loss.

3. Measures of satisfaction

- Patient's satisfaction and Care giver satisfaction

Review of Literature

Premature rupture of membranes (PROM) is rupture of fetal membranes prior to onset of regular uterine contractions. It can occur at term (≥ 37 weeks of gestation) or preterm (< 37 weeks of gestation); the latter is designated preterm PROM (PPROM).Mid trimester PROM refers to PPROM at 16 to 26 weeks.

Incidence

Premature rupture of membranes(PROM) occurs in 8% of pregnancies at term (5) , whereas PPROM and mid trimester PROM occurs at the frequency of 3 % and 1% respectively(6).In term PROM, labour occurs spontaneously in 60 % within 24 hrs of and in 95% within 72hrs. In India the incidence of PROM among all pregnant women is 7-12% of which 60% occur at term (7). Clinical chorioamnionitis occurs in 1% of all pregnancies resulting in 10 fold increase in neonatal morbidity. Chorioamnionitis is a well-recognised complication in 6-10% in women at term with prelabour rupture of membranes(8). The risk of recurrence of Preterm PROM is 16% to 32%.

In 1952, Calkins and his associates found increase incidence of maternal and morbidities due to chorioamnionitis(9). Since then expectant management has been replaced by routine induction of labour in PROM at term. Subsequently Hannah et al. measured effects of induction versus expectant management. They found that there was no significant differences in caesarean rates .They also compared induction using intravenous oxytocin with that of prostaglandinE2 gel. They concluded that induction with intravenous oxytocin was preferred method(5) due to less incidence of intrapartum and postpartum infections. A systematic review of 12

randomized trials which was done in 2006 for women at term with PROM compared expectant with active management and found that for every 50 women that underwent induction for PROM 1 case of chorioamnionitis was avoided. In 2009, Mozukerwich and associates reported lower rates of chorioamnionitis, endometritis and neonatal infection with active management(6).

PATHOPHYSIOLOGY OF RUPTURE OF MEMBRANES:

The human amnion is composed of five distinct layers contains no blood vessels and nerves.

I. Amniotic epithelial layer
II. Basement membrane
III. Compact layer
IV. Fibroblast layer
V. Intermediate layer or Spongy layer.

Amniotic epithelial layer is the inner most layer consists of amniotic epithelial cells which secrete collagen type III, collagen type IV and non-collagenous glycoproteins. Laminin, nidogen, fibronectin are non-collagenous glycoproteins. These collagen and non-collagenous glycoprotein forms the basement membrane. Compact layer forms the fibrous skeleton of the amnion present next to basement membrane. Mesenchymal cells of the fibroblast layer secrete collagens (type I and III) of the compact layer. These collagens predominantly provides the mechanical support to the amnion (11). Type V and type VI of collagens form filamentous connections between the epithelial basement membrane and the interstitial layer. There will be no interposition between amorphous ground substance and collagen

fibrils in connective tissue of the amnion at term .This helps to maintain its tensile strength. The intermediate layer that is between amnion and chorion is rich in hydrated glycoprotein and glycoproteins which give this layer a spongy appearance. This layers absorbs physical stress and helps the amnion to slide on the underlying chorion, which is adherent to the maternal decidua. Chorion is thicker than amnion resembling typical epithelial membrane and is directed towards maternal decidua. Chorion consists of cytotrophoblastic layer, basement membrane and connective tissue and is rich in collagen fibrils. However amnion has greater strength than chorion.

The balance between the synthesis and degradation of the components in extracellular matrix of the total membranes helps in maintaining their tensile strength. Any decrease in collagen content, alteration in structure of collagen and increased collagenolytic activity are associated with rupture of membranes. Membranes that ruptured prematurely appear focally defective. In intrapartum rupture of fetal membranes, it is observed that the membranes are generally weak. The site of rupture which is also known as “restricted zone of extreme morphology” is characterised as marked swelling and disruption of fibrillar collagen network within the compact, fibroblast and spongy layers of amnion.

The cause of PROM is multifactorial. Traditionally, rupture membranes has been attributed to physical stretch that weakens the membranes, however premature rupture of membranes may also result from problems with the membranal collagen namely, diminished collagen synthesis, altered collagen structure and increased collagen degradation. Hence biophysical stress and biochemical changes at the molecular level together contribute in pre labour rupture of membranes.

RISK FACTORS CONTRIBUTING TO DECREASED COLLAGEN CONTENT AND CHANGE IN STRUCTURE

Connective tissue disorders are associated with increased incidence of premature rupture of fetal membranes due to weakened fetal membranes. In 1966 Barabas et al. executed an observational study among 18 patients with Ehlers – Danlos syndrome (whose birth history was available). 13 were delivered prematurely after preterm premature rupture of membranes i.e. 72%. Ehlers – Danlos syndrome is a dramatic example of an inherited connective tissue disorder in which the basic defect lies in organisation of collagen into a stable collagen meshwork. This leads to abnormal collagen content and structure of fetal membranes causing premature rupture of membranes (12).

RISK FACTORS FOR PREMATURE RUPTURE OF MEMBRANES

Lysyl oxidase is an enzyme that initiates series of reactions for the formation collagen cross links. The collagen cross links thus formed, increase the tensile strength of fibrillar collagens. Lysyl oxidase is a copper dependant enzyme produced by mesenchymal cells of the compact layer of the membranes. Women with premature rupture of membranes demonstrated low concentrations of copper in maternal and umbilical cord serum (14).

Ascorbic acid is required for the formation of triple helical structure of collagen. Women with low concentrate ions of Ascorbic acid i.e. deficiency of vitamin c results in abnormal structure of collagen leads to premature rupture of membranes (15).

Tobacco smoking is associated with decreased serum concentrations of ascorbic acid and increases the risk of premature rupture of membranes. Also, cadmium in tobacco increases the metal binding protein metallothionein in trophoblasts resulting in sequestration of copper. Thus the decreased concentrations of both copper and ascorbic acid in smokers contribute to abnormal structure of fetal membrane collagen predisposing to risk of premature rupture of membranes (16). Even dietary deficiencies of vitamin c and copper may predispose to premature rupture of membranes..

Increased Collagen Degradation

Matrix metalloproteases are the primary enzymes responsible for collagen degradation. Degradation of collagen is inhibited by specific tissue inhibitors and other protease inhibitors. These tissue inhibitors which are metalloproteases and matrix metalloproteases form 1; 1 stoichiometric complexes and inhibit their proteolytic activity. Imbalance between the activities of matrix metalloproteases and their inhibitors, leads to an inappropriate degradation of extracellular matrixes of fetal membranes. Collagenase activity is also increased in premature rupture of membranes at term (17). Vadillo Ortega and his colleagues measured contents of collagen, acid soluble collagen, collagen degradation activity and collagen biosynthesis in 20 normal and 20 women with term premature rupture of membranes and found that collagen lytic activity and its solubility were higher in prematurely ruptured membranes. They also found that collagen synthesis was also low in these membranes.

Epidemiological data demonstrated that bacterial infection has important role in etiology of prelabor rupture of membranes. Colonization of genital tract with group B streptococci, Trichomonas vaginalis, Staphylococcus aureus, Chlamydia trachomatis, N. gonorrhoeae and the organisms that cause bacterial vaginosis increases the risk of premature rupture of membranes. These organisms release proteases that can degrade collagen and weaken fetal membranes. Thus reduces the tensile strength , predisposing to premature rupture of membranes (18). Sbarra et al. studied that fetal membranes which were infected with Escherichia coli and Group B streptococci had significantly weakened the tensile strength of the membranes compared to uninfected membranes (19). Schoonmaker et al. studied that the fetal membranes exposed to group B streptococcus, staphylococcus aureus, activated neutrophils and neutrophil elastase resulted in significant decrease in elasticity, tensile strength increasing the incidence of rupture of membranes (20). McGreger and his associates demonstrated 50% reduction of preterm labour and premature rupture of membranes in women who received treatment for bacterial vaginosis and its related infection (21).

From the above observations it is certain that any intervention that increases the risk of bacterial contamination, such as digital examination of cervix, simultaneously increases the risk of premature rupture of membranes. Lenihan confirmed that there was increased frequency of PROM after an antenatal cervical examination. He conducted a study of 349 uncomplicated term patients, 174 randomly assigned to receive weekly cervical examination from 37 weeks to delivery. In the other arm with 175 women were assigned to “no examination”

group. He found that 18% of women in the group who had weekly cervical examination had PROM compared with 6% of the "no examination" group (22).

Stretching of Fetal Membranes

Over distension of uterus due to multifetal gestation, polyhydramnios induces fetal membranal production of Prostaglandin E2, interleukin-8. Stretching of membranes also increases matrix metalloprotease activity. Prostaglandin E2 decreases collagen synthesis of fetal membranes and increases the production of matrix metalloproteases. Interleukin-8 is chemo tactic for neutrophils and stimulates collagenase activity (23). Thus physical forces induce biochemical changes in fetal membranes leading to premature rupture of membranes.

DIFFRENTIAL DIAGNOSIS:

Patient with rupture of membranes typically presents large gush of clear vaginal fluid or a steady trickle. Differential diagnosis includes urine leakage in urinary incontinence, excessive vaginal discharge; bacterial vaginosis and cervical mucus i.e. show.

DIAGNOSIS:

Early and accurate diagnosis of PROM will allow timely obstetric intervention that will decrease the serious complications, such as cord prolapse, chorioamnionitis, and neonatal sepsis.

According to 2007 American college of Obstetricians and Gynaecologists and Royal College of obstetricians and Gynaecologists (RCOG) diagnosis of Preterm Prelabour Rupture of Membranes (2006) is based mainly on patient's history and

physical examination. The minimal invasive gold standard diagnosis of rupture of membranes is based on 3 clinical signs on speculum examination.

1. Sterile speculum examination
2. Nitrazine Test
3. Microscopic ferning of cervico-vaginal discharge on drying.

Patient with rupture of membranes usually present with gush of fluid or continuous draining of urine or fluid. Sterile speculum examination helps to visualise pooling of clear fluid in the posterior fornix of the vagina or leakage from the cervix. It also provides an opportunity to look umbilical cord or fetal prolapse, cervical dilation and effacement. It also helps to obtain cultures as needed. Sometimes gross pooling is not evident, but amniotic fluid can be seen when patient coughs or strains. However diagnosis will be difficult when there is no classic gush of amniotic fluid.

For the last 75 years, there has been controversy about the optimal approach for diagnosis of rupture of membranes when there is no obvious liquor. Friedman et al first described and identified fetal particles like lanugo hair in amniotic fluid using microscope. This was later developed and published in German literature by Philip et al. However it never gained popularity because of the scant amount of lanugo hair which is usually present only in later part of pregnancy. Hence it was considered not useful for diagnosis of PPROM(24).

Subsequent diagnostic tests were developed based on cytological examination of vaginal secretions for fetal squamous cells. It is based on absence of staining of cytoplasm and nucleus of vernix caseosa compared with vaginal squamous cells. Several diverse stains are used including Masson stain, Sudan III stain, Nile blue

stain, Papanicolaou stain, pinacyanole stain, acridine orange stain. Fetal cell staining is simple, rapid, and durable with high accuracy of 97%. However glove powder contamination often resulted in false positive results as they mimic anuclear granules of fetal cells. Even hypercornified cells of vagina are also similar to anucleate fetal cells. False negatives resulted from insufficient cellular material and prolonged time interval from rupture of membranes(24).

Older cytological methods began losing popularity, because they were time consuming, required trained cytologists and were ineffective before 32 weeks and mean while many novel methods were developed. Litmus paper testing began development approximately at the same time as fetal cell staining methods. Nitrazine test is of great value. The pH of sterile urine and vaginal secretions is 5-6 and less than 4.5 respectively. The pH of amniotic fluid is 7.1 to 7.3. If the suspected fluid has pH of 7.1 to 7.3, which turned yellow Nitrazine paper to blue, and that fluid is most likely, amniotic fluid. It is associated with high false positive rates as result of contamination with blood, alkaline antiseptics, or bacterial vaginosis. False negative results can occur due to prolonged leakage or minimal residual fluid. Sensitivity and specificity of this test ranges from 90% to 97% and 16% to 70% respectively (25).

In the United Kingdom 157 pregnant women were asked to use an absorbent pad (Amniosense) that changes colour at pH > 5.2 for suspected rupture of membranes. They found that this device has a sensitivity of 98% and specificity of 65% (26).

If the same amniotic fluid is allowed to dry on a glass slide it has characteristic microscopic crystallization, termed ferning. It may give false positive results due to

finger prints or contamination with semen and cervical mucus. False negative results are due to contamination with blood or technical error. Sensitivity and specificity of this test is 51% and 70% respectively.

Amine dye test is done if conventional tests for rupture membranes are equivocal especially in PPROM, where pregnancy is remote from term and false positive diagnosis leads to unnecessary intervention. This test involves amniocentesis and instillation of indigo carmine dye into the amniotic fluid. Leakage of blue stained fluid into the vagina within 20-30 minutes and it stains tampon confirming the rupture of membranes. Some investigators consider it as gold standard for diagnosis of leaking per vaginum. However, amine dye test is an invasive procedure with inherent risks like placental abruption, infection and miscarriages.

Because of these limitations with current conventional tests and risks with gold standard tests, investigators were on a quest for an alternative and more objective test that can be a rapid, accurate, inexpensive and non-invasive. Such tests are primarily on the identification in the cervico-vaginal discharge for one or more biochemical markers that are present only in rupture of membranes but absent in women with membranes intact. Several such markers are alpha-fetoprotein (AFP), fetal fibronectin (FN), insulin like growth factor binding protein 1 (IGFBP -1), prolactin, beta-sub unit of human chorionic gonadotrophin (β-HCG), creatinine, urea, lactate, placental alpha microglobulin1 (PAMG-1).

These tests are not readily available because of cost and complexities of credentialing the providers and quality control maintaining. These tests are done

only in case of difficulty in demonstrating rupture of membranes by conventional methods but patient's history suggestive of rupture of membranes.

Amnisure is a rapid slide test that detects trace amounts of placental alpha microglobulin 1- protein in cervicovaginal secretions by using immunochromatography methods. The advantage is that, it is not affected by the trace amounts of semen or blood. The test is performed using a commercially available kit. A sterile swab is inserted into the vagina for 1 minute is then placed in a vial containing solvent for 1 minute and then the Amisure strip is dipped into the vial for next 5-6 minutes. Test results are revealed by presence of one or two lines. Presence of two visible lines suggests positive results. Presence of 1 line suggests test negative. If both the lines are absent then the test is invalid. Sensitivity of the test is around 94.4 to 98.9%. Specificity is around 87.5 to 100%.

In 2005 Cousin S M et al. compared Amnisure rapid test with standard methods for diagnosing rupture of membranes. Patients presenting with symptoms of rupture of membranes between 15-42 weeks of gestational age were included in the study. Standard conventional methods were performed to establish diagnosis and compared with Amnisure test. 203 patients are included in the study out which discrepancies between control and amnisure test occurred in 7 cases. By noting the low amniotic fluid index by ultrasound along with retesting by using both conventional method and amnisure methods positive predictive value and negative predictive value were calculated. On final analysis Amnisure test demonstrated a sensitivity of 98.9%, specificity of 100%, and positive predictive value of 100%

and negative predictive value of 99%. Therefore this is highly accurate in diagnosing rupture of fetal membranes.(27)

Actim PROM is an another easy to use immunochromatography bedside dipstick test method helps in identification of insulin like growth factor binding protein 1(IGFBP-1) in vaginal secretions. This test is currently available in India. IGFBP - 1 is secreted by placental and decidua cells present in high concentrations in the amniotic fluid. This test is not affected by the presence of infected vaginal secretions, blood, urine and semen. However it is more accurate when done as soon as rupture of membranes has occurred. This test demonstrates the sensitivity around 95-100% and specificity of 93-98%. The positive predictive value is around 98%.

A multicentre study by Darj E. et al in six departments' of obstetrics and gynaecology in Sweden was done to evaluate dipstick technique for diagnosing amniotic fluid in the vaginal secretions. Total of 174 women were examined, 46 women with obvious leaking, 29 women without rupture of membranes, 99 women with suspected rupture of membranes.44 out of 46 women with obvious PROM had positive Actim PROM test. 29 women without leaking were negative for the test, giving a sensitivity of 95.7% and specificity of 93.1%. Among the women with suspected rupture of membrane, the sensitivity was 70.8%, the specificity was 88.2% and positive predictive value 92%. They concluded that this dip stick test with monoclonal antibodies to IGFBP-1 has high sensitivity, specificity and positive predictive value complimentary to other existing methods for detecting rupture of membranes(28).

In 2011 a case control prospective study was conducted by Marcellin L et al. who compared the rapid tests for diagnosis of premature rupture of membranes based on detection of IGFBP -1 and PAMG -1 in cervico-vaginal secretions. Pregnant women between 26 and 41(6/7) weeks of gestation consulted for profuse amniotic fluid loss (group 1) or for other reasons without the rupture of membranes (group 2) were included in the study. Both Amnisure test and Actim PROM test were performed at the same visit. Amnisure test demonstrated sensitivity and specificity of 95% (82.4-99.4) and 94.8% (79.3-98) respectively and a positive and negative predictive value of 95 % (84.7-100) and 94.8 % (87.9-100) respectively. Actim Prom diagnostic test demonstrated a sensitivity and specificity of 97.5 % (85.7-100) and 97.4 % (82.4-99.4) respectively and a positive and negative predictive value of 97.5 % (88.5-100) and 97.4 % (92.5-100) respectively(29) .

In certain doubtful patients, ultrasound can be performed to look for reduction in amniotic fluid volume. If the amniotic fluid volume is normal it is unlikely that rupture of membranes has occurred. Erdemoglu et al showed that reduction in amniotic fluid index below 8cm did not reliably identify cases of suspected rupture by history with no liquor on speculum examinations. The measurement of amniotic fluid index offers no advantage over measurement of a single vertical pocket in cases where ultrasound is used to demonstrate possible rupture of membranes(30).

OTHER TESTS

Occurrence of fetal fibronectin in the cervical secretions indicates disruption of the interphase between amnion and chorion which can occur even in intact membranes. A negative test strongly suggests of absence of rupture of fetal membranes. A

positive result suggests only disruption. Sensitivity of the test is only 98% but this test has very low specificity (31).

Presence of alpha fetoprotein in the vaginal secretions suggests of rupture of membranes. Concentrations of alpha fetoprotein is high in the amniotic fluid when compared to other common secretions (vaginal secretions, semen and blood)(32). Measurement of AFP is cheaper than other commercially available tests and has a sensitivity of 98% and specificity of 100%. However blood in the vagina can give false positive results.

Other alternative markers available are those for prolactin, β- subunit of human chorionic gonadotrophin, diamine oxidase, lactate, creatinine, and urea. Assessment of these markers is based on the fact that they are present in high concentrations in the amniotic fluid compared with normal vaginal secretions. But all these tests require special laboratory equipment and training. These tests are unpopular due to cost, complexity in testing, and low sensitivity in case of equivocal rupture.

Clinical Management

Once the diagnosis is confirmed PROM at term can be managed either expectantly or elective birth usually by induction of labour. Usually in term PROM spontaneous labour occur within 24 hours (34) with 79% labouring spontaneously within 12 hours and 95% within 24 hours(35). Even with an unfavourable cervix, majority of women labour spontaneously within 24 hours(5). If spontaneous labour has not occurred within 24hours of PROM labour may be delayed up to 7 days (5) with longer latent period in nulliparous women. Expectant management involves waiting for specified period for labour to occur and then plan for induction if labour

does not occur. Expectant management of term PROM has been associated with increased risk for maternal infections such as chorioamnionitis, endometritis which may cause neonatal infections and mortality, chronic lung disease (34) and even cerebral palsy. Serious maternal morbidities has been also reported in1990 by Robson and in 1992 by Zlatnik(36). Some reports suggested that increase duration between rupture and delivery increases both maternal and fetal infections(37) even though some refute it(38). Outcome of induction of labour depends on the state of the cervix which resulting in increase length of labour and increase number of operative deliveries and caesarean section (39). Induction of labour may incur fewer costs than expectant management.

Literature reviews has conflicting conclusions regarding management of PROM at term. In 1981 retrospective study done by Johnson et al reported an increase incidence of perinatal mortality and maternal infection if time interval between rupture of membranes and delivery is more than 72 hours. They supported induction of labour(40). In 1999, Hallak found that longer the duration between leaking to onset of labour there increased incidence of neonatal intensive care unit admission, caesarean rates and more frequent maternal diarrhoea and use of analgesia (41).In 2003 crane recommended oxytocin induction as gold standard management of term PROM(42). However in 1992, Guise reported that induction of labour is associated with increased frequency of chorioamnionitis, neonatal sepsis, caesarean section and longer duration of hospitalisation. In 1997 Mozurkewich reported the risk and benefits of induction of labour, with reduced rates of chorioamnionitis, endometritis and neonatal infection.

In 1999 Akyol et al performed a prospective randomised study to compare maternal and fetal outcomes in women with premature rupture at term. 126 women were recruited in the study and were randomised to immediate induction group (Group1; n=52) and expectant group (Group 2; n=74). Expectant group was again divided into 2 groups. The first group (Group 2A; n=25) included women in whom spontaneous labour has not occurred even after 24 hrs of leaking per vaginum and then labour was induced with oxytocin. The second group (Group 2B; n=49) included women in whom spontaneous labour occurred within 24 hours. The total caesarean section was higher in group 2 i.e. 28.5% with significant P value ($p < 0.05$). The caesarean section rates in Group 1, 2A, 2B were 19.2%, 60%, and 12.2% respectively. Foetal distress rate was significantly higher with $p<0.05$. However there was no significant difference in chorioamnionitis, fever before or during labour, postpartum fever, anaesthesia, and analgesia. Women in group 1 went into active labour sooner, had fewer vaginal examinations and delivered early with short hospital stay than those in group 2 with a significant difference (*p value* < 0.05). There was significant difference in babies receiving antibiotics, NICU admissions and babies requiring ventilation after initial resuscitation in Group 2A when compared to Group 1. However the overall incidence of neonatal morbidity was not significantly different. They concluded that induction of labour does not increase number of caesarean sections compared to expectant management, therefore it will be the best policy to induce labour immediately (43).

In 1992 Cheng et al (44)randomised 59 women at term with PROM to receive either intra-vaginal prostaglandin E2 (3mg) or sterile K-Y jelly(placebo). These women were observed for 24 hours without intervention unless clinical situation

demanded for it. Induction or augmentation with oxytocin started only after 24 hours of conservative management. Women who received prostaglandin went into labour earlier within 1270 minutes compared to 1700 minutes in women who received K-Y jelly. Women in prostaglandin arm delivered earlier than placebo. The incidence of febrile episodes were significantly higher (>37.5^{o}C) in both intrapartum and postpartum periods in women who received prostaglandins. But none of them required antibiotics. There was no significant difference in neonatal outcome in both groups. They concluded that, early intervention with intra-vaginal prostaglandin E2 gel confers no advantage compared with conservative management except for duration of labour.

A prospective randomised controlled trial done in 1992 by Mahamood et al compared conservative management versus prostaglandin E2 in 230 primigravidae women with premature rupture of membranes at term. 115 women were randomised to active management with prostaglandin E2 2mg. After 6 hours 1 mg prostaglandin E 2 was instilled in posterior fornix if there was no uterine activity. Another 115 women were randomised to conservative management, admitted in the ward for observation for 24 hours. Escalating dose of oxytocin was started in both the groups, if labour does not occur in 24 hours. They found that 32(29%) of women in conservative group and 3 (3%) in prostaglandin E2 had no evidence of contractions even after 24 hours of admission with (95% CI 14-40, $p < 0.001$.). The use of prostaglandin significantly reduced the time interval between PROM and onset of labour between PROM and oxytocin augmentation and PROM and delivery. There was no significant difference in number of caesarean sections ($p>0.05$). There was no significant difference in the requirement of oxytocin

augmentation in both the groups (difference 17%; 95%CI 5 – 34). Three babies of prostaglandin E2 group and 1 baby in conservative management group were admitted in NICU for hypoxia (95% CI 9 -13). Hence they concluded that early use of prostaglandin is associated with a significant reduction in PROM to delivery interval without a significant increase in caesarean section rate or neonatal or maternal infective morbidity. However, the advantages associated with conservative approach should not be overlooked.

In 1995 Mahamood et al (45) compared conservative management in parous women with premature rupture of membranes to the use of prostaglandin E2 at term. 100 parous women were randomised, of which 50 were treated conservatively for 24 hours and other 50 were actively managed using PGE2 gel (1 mg). First dose was administered at the time of admission and repeated after 6 hours if labour was not established. Both groups received intravenous oxytocin if uterine activity has not occurred within 24 hours after admission. They demonstrated significant reduction in the mean duration of time from PROM to onset of labour: 17.26 +/- 1.51 hours in the conservative group versus 6.50 +/- 1.23 in the PGE2 group. A significantly smaller proportion of women required oxytocin in the PGE2 group (12 versus 38%, $P < .02$). The analgesic requirements of the two groups were comparable. Within 24 hours of PROM, 80% of the women in the Prostaglandin E2 group and 56% in the conservative group had delivered ($P < .02$). 96% of those managed conservatively and 100% of those managed actively with PGE2 has delivered vaginally. Hence author concluded that active management using PGE2 gel in parous women with premature rupture of membranes significantly improves

the time to delivery without effecting the caesarean rate or maternal and fetal infective morbidity.

In 1995 Natale R. et al (46)randomly allocated 262 women into the expectant and active management groups with the hypothesis that the expectant management in women with premature rupture of membranes at term would result in a lower caesarean birth rate with no increase in maternal, fetal, or neonatal infection. All term patients with premature rupture of membranes were randomly allocated either to expectant management for 48 hours or to active management with oxytocin after confirmation of leaking. Patients who were randomized to expectant management were not examined vaginally until they went into labour. Patients randomized to induction of labour group had induction with oxytocin after 8 hours of rupture of membranes. They found that there was no significant difference in caesarean birth rate and the clinical endometritis in both the groups. Pathologic diagnosis of chorioamnionitis and funisitis was significantly greater in the expectant management group ($p < 0.05$). Eight of the 15 babies with funisitis were admitted to the neonatal intensive care unit (2, in the induction of labour group and 6, in the expectant management group, $p < 0.05$). They concluded that expectant management did not reduce the incidence of caesarean birth. However it was associated with increased incidence of pathologic diagnosis of funisitis .There were significantly increased neonatal intensive care unit admissions of the new born in the expectant group.

Shalev et al in 1995 has done a prospective, nonrandomized study, 566 low risk women with singleton term pregnancies with no other risk factors with PROM

were assigned to either 12-hours or 72-hours expectant management groups. Women who had not entered labour in both the groups after assigned period were induced with oxytocin. The infectious complications and method of delivery were compared with regard to infectious in both the groups. There was no statistical difference in the rate of chorioamnionitis between both the groups (11.7 versus 12.7%; relative risk [RR] 0.9, 95% confidence interval [CI] 0.6-1.5; P =0.83). There was no significant difference observed in the number of caesarean sections (4.7 versus 6.7%; RR 0.7, 95% CI 0.3-1.4; P = 0.39). 55% of the 12-hour group underwent oxytocin induction, compared with 17.5% of women in the 72-hour group (RR 5.8, 95% CI 3.9-8.5; P <.001). Women who had induction after 72-hours of expectant management were associated with increased risk of caesarean deliveries compared with those after a 12-hour expectant group (RR 5.9, 95% CI 2.3-15.1; P < .001). Overall, women in the 12-hour group had shorter admission-to-discharge interval than the 72-hour group (5 versus 6 days, 95% CI of the difference 0.6-1.3; P < .01). They concluded that infectious complications and mode of delivery are comparable. But longer waiting period prolongs the delivery interval and hospital stay and increases cost.

In 1996 TERMPROM (Term Prelabour Rupture of Membranes)(5) study was done to determine whether practice of active management is better than expectant management. In this study they also compared methods of induction of labour. Women were randomly assigned to four groups either immediate induction of labour with oxytocin / prostaglandin E2 gel or expectant management for 4days. Women in expectant management were induced after 4 days if there was no uterine activity or earlier if a complication occurs. Women in expectant management were

also randomised for induction of labour to either oxytocin group or prostaglandin E2 group. The neonatal infection rates were 3% for induction with prostaglandin group, 2% for induction with oxytocin group, 2.8% for the expectant oxytocin group and 2.7% for expectant prostaglandin group. The caesarean section rates were 9.2 to 10.6%. The rate of clinical chorioamnionitis is higher in expectant oxytocin group compared to immediate induction group (8.6% Vs 4%, P< 0.01). There was higher rate of post-partum fever in expectant group compared to active management group (3.6% vs. 1.9%; P=0.08). They concluded that neonatal infections and number of caesarean sections are comparable in both groups. But maternal morbidity in terms of chorioamnionitis and endometritis was little higher than in the expectant group. They also found that women view induction of labour more positively than expectant management.

Because of these conflicting conclusions from the literature available two authors Dare MR.middleton and Varathuaraju B independently reviewed 12 trials after assessing the each trial quality. The extracted data and the results were published in Cochrane Database Reviews 2006(47). These trials compared planned early delivery versus expectant management for women with premature rupture of membranes at term. They found that there was no significant difference for the mode of delivery in both the groups (6814 women in 12 trials: RR 0.94, 95% CI 0.82 to 1.08). Relative risk for operative vaginal birth was 0.98% with 95% CI 0.84 to 1.16(7 trials, 5511women). Fewer women in the planned management groups had significantly less chorioamnionitis compared to expectant management groups (9 trials, 6611 women, RR 0.74, 95%CI 0.56-0.97). There was no significant difference observed for neonatal infections (9 trials, 6406 infants: RR 0.83, 95%

CI 0.61 to 1.12). However admissions to NICU were more in planned management group (5 trials, 5679 infants, RR 0.72, 95% CI 0.57 to 0.92). A significant number of women in planned management group viewed their care more positively when compared to expectant management. Hence, the authors concluded that as there was not much difference in both the groups, women can be given all the required information to make their own choice.

ACOG 2016 recommends to induce labour in women with PROM at 37 0/7 weeks of gestation or more, if not in labour at the presentation (48). Intra-vaginal PGE2 appears to be safe and effective for induction (ACOG guideline induction of labour 2009)(49). It is considered a safe and effective method.

Society of Obstetrics and Gynaecology of Canada (SOGC) recommends to consider vaginal PGE2 for immediate induction of labour in women with premature rupture of membranes(Induction of labour updated in 2015)(50).

World Health Organisation (WHO) 2011 recommends induction of labour within 24 hours of rupture of membranes. It considers use of oxytocin as first option for induction of labour for premature rupture of membranes (51) compared to other methods of induction.

According to National Institute for Health and Care Excellence(NICE) women with prelabour rupture of membranes at more than 34 weeks should be offered a choice of expectant management or induction of labour with prostaglandin E2 .They consider induction as appropriate only after 24hrs of rupture of membranes(52). They (NICE 2008- 2013) found no evidence to recommend appropriate method of induction of labour. The guidance development group (GDG) recognised the

benefit from the wide spread use of intra vaginal use prostaglandin E2 for the last twenty years in women with premature rupture of membranes. GDG also considered it as less invasive than intravenous oxytocin which requires continues access and continuous monitoring of fetal heart. It also restricts the mobility. After considering above facts GDG considered prostaglandin E2 as a preferred method of induction of labour(49).

Intravenous oxytocin is the traditional method for inducing labour in premature rupture of membranes, however this method has been found to be associated with significant increase in the incidence of instrumental deliveries and caesarean sections in some of the studies(39). Induction with prostaglandins followed by oxytocin has been used for the last 2 decades and presently considered as gold standard in women with premature rupture of membranes.

To assess the effects of early stimulation of uterine contractions after premature rupture of membranes after 34 weeks by prostaglandins with or without need of oxytocin versus oxytocin alone, a systemic review was done in 1996 by Hannah ME and Tan BP. They included seventeen trials irrespective of quality which assessed effects of early stimulation of uterine contractions with prostaglandins and oxytocin. They looked at incidences of perinatal mortality and morbidity, obstetric intervention and maternal condition. Based on eight trials there was increased incidence of chorioamnionitis (Odds ratio 1.49, 95% CI 1.07 to 2.09) and neonatal infections (odds ratio 1.63, 95% confidence interval 1.00 to 2.66). In prostaglandins group compared to oxytocin group. There was increased incidence of nausea and vomiting in women prostaglandin groups. There was no significant difference in rates of caesarean section, endometritis and perinatal mortality in both the groups.

Based on four trials they found that prostaglandins are associated with decreased in rate of internal fetal heart rate monitoring and epidural analgesia (Odd's ratio 0.86,95% CI 0.73-0.98)(53).

This review was initially published in august 1998. Most recent amendment was done in 2000 which included 8 trials. Trials included in this meta-analysis showed no evidence that induction with prostaglandins increases or decreases rate of caesarean sections as different forms of prostaglandins (vaginal, intracervical, oral PGE2/ intravenous PGF2 alpha, / vaginal PGE1) are used in this trial and it was not appropriate to combine these trials. Reviewers concluded that women with pre-labour rupture of membranes after 34 weeks should be offered to choose the treatment option after informing the benefits associated with induction of labour with prostaglandins (lower risk of epidural analgesia and internal fetal heart rate monitoring) as compared to the risks associated with it (increased risk of chorioamnionitis, maternal nausea, vomiting, need of multiple vaginal examinations , neonatal morbidity like infections and need antibiotics and NICU admissions).

PROSTAGLANDINS

Prostaglandins are a group of long chain fatty acids containing 20 carbon atoms including a 5 carbon ring derived from arachidonic acid which is present in all nucleated cells. They have both autocrine and paracrine action. Prostaglandin E2, prostaglandinF2α, prostaglandin E1 is the main prostaglandins that are used for labour induction. All three of them have potent oxytocic effects on the pregnant uterus. Since 1960's prostaglandins have been used for induction of labour. They

have been widely studied and used for ripening of cervix. They cause ripening of the cervix by altering the ground substance and increase collagenase activity. They also cause an increase in hyaluronic acid, dermatan sulphate and glycosaminoglycan and elastase activity in the cervix. Prostaglandins also cause myometrial contractility by increasing intracellular calcium levels. Apart from the uterus and cervix they act on several target organs causing side effects like nausea, vomiting and diarrhoea and fever. They are easily metabolised in the body by conversion of the 15-hydroxy group to ketones by the enzyme 15- hydroxyl-prostaglandin dehydrogenase.

PROSTAGLANDIN E2

Dinoprostone is synthetic analogue of prostaglandin E2 In US a gel, a time release vaginal insert, and 10mg suppository are three commercially available in forms. Local administration of dinoprostone is used for cervical ripening. Prepidil is a gel form available in 2.5ml syringe containing 0.5mg of dinoprostone. The prefilled syringe is placed intracervically just below the internal os. Women should be in reclined position for at least 30 minutes. Dose can be repeated once in six hours in 24 hours.

Cervidil is a 10mg a time release vaginal insert approved for cervical ripening. The insert provides slower release 0.3mg/hr than gel form. It is placed transversely in the posterior vaginal fornix. Lubricant should be used sparingly as it will hinder drug release. Women should be in recumbent position for at least 2 hours. Insert should be removed after 12 hours or earlier if labour sets in. Oxytocin should be started only after 30 minutes of removal of the vaginal insert.

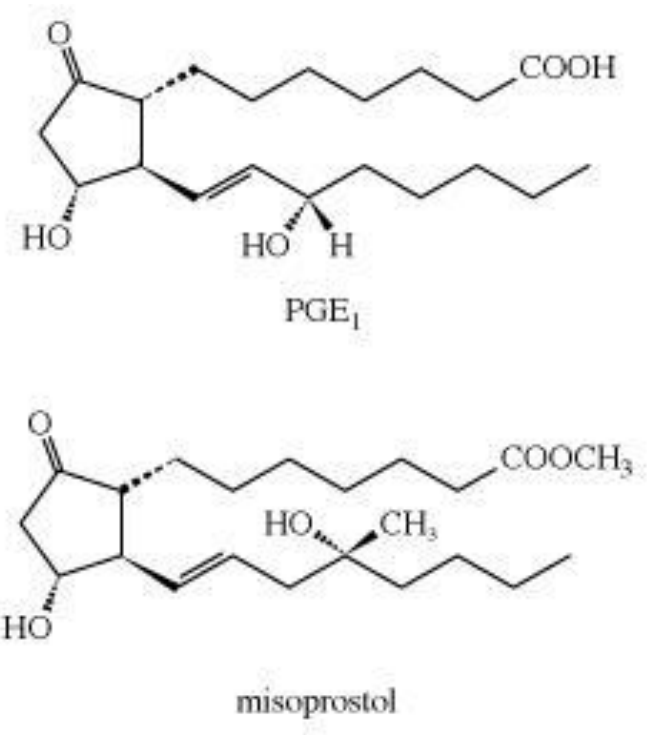
Most of the meta-analysis demonstrated reduced time to delivery within 24 hours. A 2009 Cochrane review of 63 trials by Kelly and co-workers reported higher delivery rate within 24 hours with vaginal prostaglandins E2 when compared to placebo or no treatment. But the rates of caesarean deliveries are unchanged. But they also concluded that women who were induced with prostaglandins E2 for premature rupture of membranes has increased occurrence of maternal and neonatal morbidity(54) 2008 Cochrane review by Boulvain and his associates compared vaginal and intracervical PGE2 in terms of hyper stimulation with or without heart changes for induction of labour with intact membranes and found no significant difference but the risk of not attaining vaginal delivery within 24 hours is increased with intracervical PGE2(55). Hence it recommended that intravaginal PGE2 preferred to intracervical PGE2. Prostaglandin E2 has to be stored in a refrigerator at 20 ^{0}C and it has to be brought to room temperature. It is costlier than prostaglandin E1. Cerviprime and Dinoripe are gel forms available in India. PG and primiprost are tablet forms available in India.

Prostaglandin E1

Synthetic analogue of Prostaglandin E1 is misoprostol and its chemical name is 15 deoxy -16-hydroxy-16-methyl-Misoprostol. It was used mainly as treatment for gastric and duodenal ulcers which were caused by non-steroidal anti-inflammatory drugs. It was used for first and second trimester abortions and for ripening of the cervix before induction of labour. It has been approved by the Food and Drug Administration for its usage in gastric ulcer but not for obstetric use. It is marked under trade name “cytotec” used in treatment of peptic ulcer disease .Misoprostol

is cheap with fewer side effects compared to other prostaglandins. Prostaglandin E1 is stable at room temperature.

Misoprostol differs structurally from other prostaglandins with the presence of methyl ester at C-1, a methyl group and hydroxyl group at C-16 instead of C-15. The anti-secretory potency and duration of action increased to presence of methyl estates at C-1. Movement of hydroxyl group from C 15 to C-16 and addition methyl group at C-16 improves oral activity and increases duration of action and improves safety profile of misoprostol(56).



Structure of Misoprostol

Pharmacokinetics of Misoprostol

Misoprostol initially developed for oral administration. Other routes of administration are vaginal, rectal, sublingual and buccal. These routes are also been extensively used in obstetrics and gynaecology. Pharmacokinetic properties have been looked at for all the routes in several studies. The peak concentration time (Cmax), time to peak concentration (Tmax) and the area under the serum concentration versus time curve (AUC) were studied. Cmax and Tmax denote how well the drug is absorbed. AUC denotes total exposure to drug

ORAL ROUTE

After oral administration the drug misoprostol rapidly gets absorbed. It undergoes rapid first pass metabolism and forms misoprostol acid. The time to peak concentration of misoprostol is 12 +/- 3minutes. The mean plasma value of misoprostol is directly related to the dose of the drug taken. The peak concentration of the drug decreases if misoprostol is taken with food or antacids. Cmax of misoprostol when taken on empty stomach is 811+/-317pg/ml and where as it is around 303 +/- 176pg/ml with T max is around 14 +/- 8minutes when taken with food . This difference is statistically significant. Serum binding of misoprostol is less than 90% and its therapeutic action is independent of the serum concentration.

Oral misoprostol had quicker onset of action 8 minutes with higher peak concentration when compared to vaginal route. Duration of action of misoprostol is approximately 2 hours. The area under curve is only 54% of the sublingual administration of the drug(57).

Route of administration	Onset of action	Duration of action
Oral	8minutes	2 hours
sublingual	11 minutes	3 hours
vaginal	20 minutes	4 hours
Rectal	100minutes	4 hours

Vaginal Route:

Vaginal misoprostol has a slower absorption rate with longer duration of action . The peak concentration is around 80 minutes i.e plasma level reaches a peak in 70 - 80 minutes and then slowly declines with drug detectable upto 6 hours. The absorption of vaginal misoprostol is inconsistent. It depends on the dose and pH of vaginal secretions and therefore is different for every woman. Some times tablet will be still in the vagina after several hours of administration suggesting of incomplete and variable absorption. Moistening the medication with water before administration has proved to be non-beneficial (58)

Sublingual Route

Tablet misoprostol completely gets absorbed when kept under the tongue within 20 minutes. Time to peak concentration of the drug through this route is shortest. Sub lingual administration has highest peak concentration and greatest bioavailability when compared to other routes. Compared to oral misoprostol sublingual route has a similar Tmax but a higher Cmax. It has higher bioavailability as it does undergo first pass metabolism. Due abundant blood supply below the tongue with neutral pH also helps in rapid absorption which in turn increases bioavailability.

Other routes

Here the tablet is placed between the teeth and the cheek. The highest peak concentration is achieved in 75minutes like vaginal misoprostol but the bioavailability is less when compared to vaginal route(59). Rectal misoprostol is widely used in the management of postpartum haemorrhage. The time of peak concentration of rectal misoprostol is 40 -65 seconds. Absorption of drug through this route is similar to vaginal route with area under curve less than $1/3^{rd}$ of vaginal route(59).

Misoprostol is mainly excreted by kidneys. However dose adjustment is not required inpatients with renal impairment but the dose. Dose can be reduced if patient is not tolerating the usual dose. In women who received oral misoprostol for postpartum haemorrhage drug was found in the breast milk within 30 minutes of administration and the peak concentration occurs in 30 minutes. Levels became undetectable after 4-5 hours.

Pharmacodynamics:

Misoprostol was initially was used for protection against the effect of NSAIDS's on the gastric mucosa , for its anti-secretory and mucosal protective actions and its effects on uterus and cervix was considered as side effects. Later this was widely studied on pregnant uterus and found that misoprostol acts on the prostaglandin receptors of the uterus and cervix.

Adverse effects: Use of misoprostol in third trimester for induction of labour is associated with hyper stimulation , tachysystole , passage of meconium and

meconium staining liquor, and caesarean delivery for fetal distress and perinatal morbidity(59).

Other common side effects that diarrhoea, vomiting and nausea which are self limiting(60).

There are number of methods of induction of available. Prostaglandins are single most effective method of induction of labour when combined with amniotomy in women with intact membranes. Prostaglandin E2 is registered in many countries for use of induction of labour. As prostaglandin E2 was extensively studied ACOG 2009, NICE 2013 and SOGC2015 recommends prostaglandin E2 as preferred method of induction of labour for premature rupture of membranes at term.

Disadvantages of Prostaglandin E2:

Even though Prostaglandin E2 is available in many countries it is expensive drug, which is not stable at the room temperature. It has to be stored in refrigerator. It cannot be used in women with high parity.

Advantages of Misoprostol :

Drug is inexpensive. It is stable at room temperature. It can be administered any these routes: vaginal, oral, sublingual, buccal and rectal. These properties make misoprostol ideal for induction of labour especially where storage facilities not available or financial constraints exists.(61)

Alfirevic et al reviewed data (Cochrane review June 2014) of 76 clinical trials comparing oral misoprostol with other methods of induction of labour at term. In nine trials which compared oral misoprostol with placebo demonstrated that

women using oral misoprostol were more likely deliver vaginally within 24 hours (RR 0.16, 95% CI 0.05 to 0.49; one trial), need for less oxytocin (RR 0.42, 95% CI 0.37 to 0.49) and with decreased caesarean section rate (RR 0.72, 95% CI 0.54 to 0.95).

They also reviewed 12 trials comparing oral misoprostol with vaginal dinoprostone women given oral misoprostol had lesser caesarean section rate (RR 0.88, 95% CI 0.78 to 0.99). The rate of caesarean section was significantly lower in women who received oral misoprostol (RR 0.77, Thirty-seven trials compared oral and vaginal misoprostol and found no statistically significant difference in the primary outcomes of maternal morbidity /mortality and neonatal morbidity and mortality. The results for vaginal delivery within in 24 hours, hyper stimulation and caesarean section were highly heterogeneous. Hyper stimulation with FHR changes was dose related. Lower doses of oral misoprostol were associated with less hyper stimulation. However only few babies had low Apgar score in the oral group (RR 0.60, 95% CI 0.44 to 0.8) and also associated with decrease in postpartum haemorrhage (RR 0.57, 95% CI 0.34 to 0.95)(49)

Hence in this review Alfirevic and his associates concluded that oral misoprostol for induction of labour is effective at achieving vaginal delivery within 24 hours and is more effective than placebo. Oral misoprostol as effective as vaginal misoprostol and had fewer caesarean sections when compared with vaginal dinoprostone or oxytocin. Evidence supports oral misoprostol is safer than vaginal misoprostol. . This is especially more appropriate in conditions where the risk of ascending infection is high and the lack of staff where women cannot be intensely monitored.

Hence premature rupture of membranes can be considered as an ideal situation where oral misoprostol can be used for induction of labour.

In 2014 August commentary by Abdel-Aleem H (WHO RHL) recommends oral misoprostol 20-25µgm two hourly as first line option for induction of labour. And found to be more safer and effective method than 25µgm of vaginal Misoprostol. He reviewed 3 systemic reviews and concluded that vaginal misoprostol is associated with hyper stimulation more than oral administration(61).

Comparison of Misoprostol with other regimens of active management:

Comparison with placebo

Cheung et al. in 2006 compared the efficacy of 2 different doses (50 and 100 micrograms) of oral misoprostol in induction of labour with placebo in premature rupture of membranes. It was found that both the doses were equally efficient in nulliparous women in reducing the delivery time interval and duration of labour but the same effect was not observed in the multiparous group. This was similar done by Hoffmann et al in 2000 when he compared 47 patients receiving 100 mcg every 6 hours of misoprostol with 49 patients receiving Vitamin C (placebo) and found that oral misoprostol is effective in patients with PROM with no significant differences in incidences of maternal and neonatal morbidities. In 2007, Levy et al along with the above finding found that misoprostol significantly reduced the need of oxytocin and the need for antibiotics. This was done in a randomized controlled trial with 64 patients receiving 50mcg of oral misoprostol every 4 hours and 66 patients receiving placebo.

Comparison with PGE2.

Oral misoprostol is effective and a safer method for labour induction in patients with PROM at term. This was concluded in two different studies done in 2003 and 2009 by Hussaini et al and Nagpal et al respectively. In settings where repeated vaginal prostaglandin E2, prolonged expectant management, and a high rate of caesarean deliveries cannot be afforded, oral misoprostol led to a shorter induction-to-delivery interval and a smaller proportion of women requiring oxytocin augmentation.

Comparison with oxytocin

Butt et al. in 1999 compared induction to delivery interval between oral misoprostol (50mcg every 4 hrs) and intravenous oxytocin and found that oxytocin was effective and resulted in shorter induction-to-delivery interval. Nagi et al. in 2000 and Shabana et al. in 2014 did a similar trial and found that 100 mcg of oral misoprostol every 4 hours was more effective in reducing the duration of labour in nulliparous women. These findings were challenged by Mozurkewich et al. in a multi-centric randomized control trial done in 2003 comparing 100 mcg of oral misoprostol every 6 hours with oxytocin. It was found that there was no difference between the two groups taking the end point of induction-to-delivery interval and number of caesarean sections; and the results of Nagi et al. could be due to the shorter dose interval.

Maternal Complications associated with Prelabour rupture of membranes

PROM is associated with increased risk of chorioamnionitis and endometritis. Frequent vaginal examinations and meconium stained liquor increased risk of above mentioned complications.

Chorioamnionitis: Clinical chorioamnionitis occurs in 1% of pregnancies. Signs and symptoms of chorioamnionitis are maternal fever of more than 38 degree centigrade, maternal fever, maternal or fetal tachycardia, foul smelling liquor, purulent amniotic fluid.

Endometritis: Generally endometritis occurs after 2-3days of delivery. Endometritis is characterised by fever, foul smelling lochia, lower abdominal pain, sub involution of uterus and uterine tenderness.

Neonatal complications associated with Prelabour rupture of membranes

Fetal complications associated with premature rupture of membranes are cord prolapse, cord compression and neonatal infection. 2 to 2.8% are associated with neonatal sepsis. Clinical presentation varies which may include diminished activity, poor sucking, bradycardia, temperature instability, irritability, jitteriness, vomiting, diarrhoea, abdominal distension, seizures, .jaundice. Diagnosis of neonatal sepsis is based on clinical and culture. As membranes rupture bacteria ascend into uterine cavity causing neonatal sepsis.

Intrapartum antibiotics in women with premature rupture of membranes are recommended in following conditions.

- Positive screening culture for Group B streptococci from either vagina or rectum.
- Positive history of previous infant with early-onset Group B streptococci disease.
- Antenatal urine culture with Group B streptococci. Intrapartum fever (≥100.4ºF, ≥38ºC) /Prolonged rupture of membranes (≥18 hours).

Cochrane data base review in 2002 found no significant differences in maternal and neonatal outcomes in women who received prophylactic intrapartum antibiotics(62). But in women with leaking more than 12 hours, prophylactic antibiotics are significantly reduced the occurrence of chorioamnionitis by 51% and endometritis by 88% (63)

Ambulation

Even though there is no evidence that recumbent position in labour is more advantageous for women or new born, than the upright position, it is the preferred method in most health care centre as it is convenient for health care professionals who are attending to the deliveries. But most of the observational studies suggest that the recumbent position decreases placental blood flow, impedes progress of labour and has adverse effects on contractions.

Two review authors independently reviewed 25 trials which compared upright and ambulant positions to recumbent position during the first stage of labour and the results were published in a Cochrane systemic review 2013.They found that the first stage of labour was approximately 1 hour and 22 minutes shorter for women in upright

position than women in recumbent positions (average MD -1.36, 95% CI -2.22 to -051). They also found that women in upright position had lesser caesarean sections (RR 0.71, 95% CI 0.54 to 0.94) and lesser requirements of epidural anaesthesia (RR 0.88 95% CI 0.66 to 0.99). Even the number of neonates admitted in neonatal ICU was lesser in the upright group. There were no significant differences in second stage of labour(64). Present protocols which require intravenous Oxytocin compels the patient to be in the recumbent position and therefore Oral misoprostol would be the ideal supplement for the same.

METHODOLOGY

This study was a prospective randomized controlled unmasked trial comparing safety and efficacy of oral misoprostol with intravenous oxytocin for induction of labour in prelabour rupture of membranes at term. This trial was conducted between February 2016 to August 2016.The study protocol was reviewed and approved by the Institutional Review Board , Christian Medical College and Hospital, Vellore.

Term pregnant women with prelabour rupture of membranes admitted to the labour room of the Obstetrics and Gynaecology department of the Christian Medical College and Hospital, Vellore were recruited in the trial.

All the patients with leaking per vaginum at term were recruited in the trial if they fulfilled the following criteria:

Inclusion Criteria:

- Pregnancies between 37- 41 weeks of with singleton foetus with vertex presentation.
- Reassuring foetal heart rate.
- Definite diagnosis of PROM

Exclusion Criteria include:

- Contraindications to vaginal delivery.
- Previous uterine scar
- Diagnosis of labour
- Clinical estimated fetal weight more than 4 kilograms
- Evidence of temperature >100.4degree Fahrenheit, uterine tenderness or foul smelling amniotic fluid.

- Any medical diseases like diabetes on insulin or severe pre-eclampsia

Informed written consent was taken from all the women recruited in the study. After informed consent, women were assigned to a induction method by opening sequentially numbered opaque sealed envelopes. These envelopes contain labels indicating study allocation. Permuted block randomization of sizes 2, 4 or 6 were used randomly to allocate the method of induction to the subjects. These envelopes were prepared by statistician (Biostatistics department, CMCH, Vellore) not involved in patient care.

Thus the women were randomized to receive either

A) Oral misoprostol

B) Intravenous oxytocin

In women who were randomized to oxytocin group vaginal examination was done to assess Bishop's score. In this group Oxytocin was started as per the labour room protocol of Christian Medical College Hospital, Vellore. The protocol followed was:

- Intravenous line was started without oxytocin and when stabilized to 4 drops per minute, 2.5 units of oxytocin were added to 500 ml of normal saline or ringer lactate (crystalloid solutions).
- The bottle of fluid was labelled with the concentration of oxytocin.
- To avoid bolus administration, infusion was started into the main intravenous line close to the venipuncture site.
- The starting dosage of oxytocin infusion at 4 drops per minute (2 milli units) with increments of 4-8 drops per minute every 20-30 minutes was undertaken only if uterine contractions are inadequate (3 contractions in 10 minutes).
- Fetal heart rate, uterine resting tone, frequency, duration and force of contractions was monitored.

- Oxytocin infusion was discontinued immediately in the event of uterine hyperactivity or fetal distress.
- The maximum dosage was limited 7.5units in 500ml of crystalloid to 60 drops per minute.

Women who were randomized to the oral misoprostol group were given 50µg of drug orally at the interval of 4 hours up to a maximum of 3 doses in nulliparous and maximum 2 doses in multiparous. However vaginal examination was not done in this group before administration of each dose of oral misoprostol. Every 4 hours, next dose of the drug was administered only if there were no contractions or pain. After four hours of the last dose, i.e. three doses in nulliparous and two doses in multiparous, vaginal examination was done, Bishop's score was assessed and labour was augmented using oxytocin as required. Contractions were monitored and labour was allowed to progress. Repeat vaginal examination was done every 4 or 6 hours to assess progress in labour depending on whether the patient is in latent or active phase of labour.

If the woman complains of pain or if there were documented contractions at the time of next scheduled dose, further doses misoprostol were withheld. At that time, pervaginal examination was done and oxytocin augmentation was initiated as required. Vaginal examination was done only after 4hrs of maximum doses or earlier if there was pain, contractions, non-reassuring fetal status, or delivery. All women in both the groups had continuous fetal heart rate monitoring using the cardiotocogram. All further interventions were left to the discretion of the treating obstetrician.

Regular uterine contractions were defined as more than 3 contractions in 10minutes, each lasting for more than 20 seconds. Uterine hyperstimulation was defined as more than 5 contractions with changes in fetal heart rate. Fetal heart was considered to

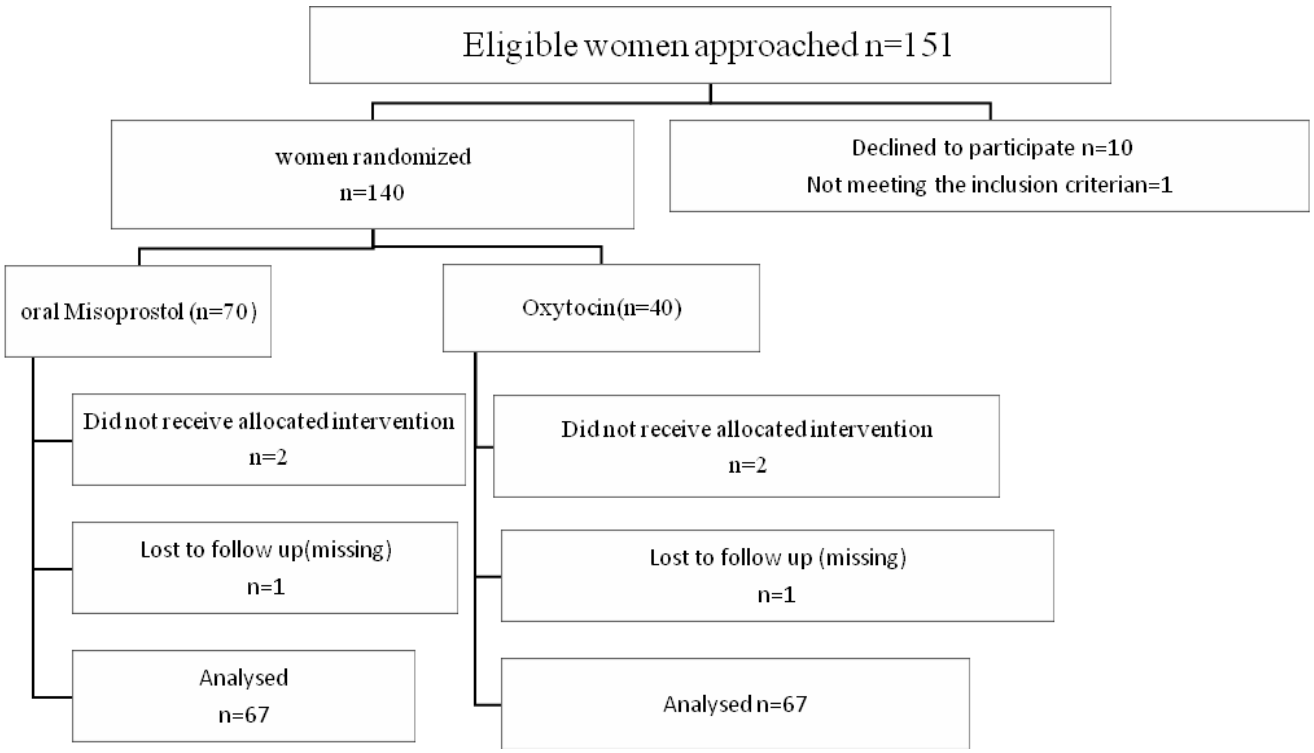
be non reassuring if there were recurrent decelerations (early, variable, late), fetal bradycardia (Basal heart rate on cardiotocography is less than 100beats per minute lasting for more than 3 minutes), fetal tachycardia (Basal heart on cardiotocography is more than 160beats per minute).More than

The primary outcomes were time period from induction to delivery, percentage of women delivered vaginally within 24 hours of induction and the rate of caesarean section. Secondary outcomes that were evaluated are measures of effectiveness with need for oxytocin administration. Other secondary measures were neonatal morbidity or perinatal death, serious maternal morbidity or death, APGAR score less than 7 minutes at 5minutes of birth, neonatal intensive care unit admissions ,maternal nausea, vomiting , diarrhoea, fever and post partum haemorrhage more than 500ml. Women satisfaction and care giver satisfaction were also considered.

SAMPLE SIZE : A sample of size of 200 (100 in the misoprostol group and 100 in the intravenous oxytocin group) was calculated to detect a mean difference of 2 hours in induction to delivery time between two groups with 80% power ,using 2 sample t-test and assuming 5% level of significance and a standard deviation of 5 hours. The mean induction to delivery time was assumed to be 12 hours and 14hours respectively.

RESULTS

Of the 150 eligible women approached, 10 women declined to participate in the study. Total of 140 women were randomised into oral misoprostol and oxytocin groups with70 in each arm. Two in the misoprostol group did not receive the allocated intervention as the care giver was not willing to continue for one patient and the other did not receive as it was a breech presentation. Two in the oxytocin group did not receive the allocated intervention as liquor was meconium stained for 1 and the other woman had a transverse presentation.2 patient charts 1 in each arm were missing and data could not be collected. Total of 134 womenwere analysed in this study with 67 in each arm.



Demographic Characteristics:

Women in both groups showed no difference in base line characteristics prior to treatment.

There was no significant difference in age, height, weight and BMI of both the groups.

Table 1:

Baseline Characteristics	Total n=134 Mean (S.D.)	Oral misoprostol n=67 Mean (S.D.)	Oxytocin n=67 Mean(S.D)	p value
Age in Years	26.05 (3.64)	25.64 (3.64)	26.64 (3.62)	0.192
Height in cms	157.29 (6.81)	156.63 (6.74)	157.96 (6.86)	0.260
Weight in Kg	69.53 (10.91)	68.87 (10.68)	70.19 (11.18)	0.486
BMI (kg/m2)	28.11 (4.02)	28.11 (4.26)	28.10 (3.80)	0.984

Gestational Age

The women in this study were in between 37 to 41 weeks of gestational age.

The mean gestational age in oral misoprostol group was 38.45 and in oral group was 39.7.

There was no difference in gestational age in both the arms.

Table 2:

Group	Mean(S.D.)	Minimum	Maximum
Oral Misoprostol	38.45(0.98)	37	40.4
oxytocin	38.70(0.86)	37.20	40.4

Distribution of Parity

There were 106 nulliparous, 23 primiparous and 58 multiparous in the study inclusive of both the groups. In misoprostol arm 74.63% were nulliparous, 20.90% were primiparous and 4.48% were multiparous. While in oxytocin group 56% are nulliparous. 9% are primiparous and 2% are multiparous. There was no significant difference in both the arms.

Table 3:

Parity	Total (%)	Oral misoprostol (%)	oxytocin	
Nulliparous	106(79.10)	50(74.63)	56(83.58)	p value 0.443
Primiparous	23(17.16)	14(20.90)	9(13.43)	
Multiparous	5(3.73)	3(4.48)	2(2.99)	

Obstetric Medical Complications:

	Oral misoprostol group (%)	Oxytocin group (%)	Total (%)	p value 0.858
GDM on diet	10 (14.93%)	14(20.90%)	24 (17.91%)	
PIH	1 (1.49%)	1(1.49%)	2 (1.49%)	
Others	4 (5.22%)	3 (4.48%)	7 (5.22%)	
Nil	52 (77.61%)	49 (73.13%)	101(75.37%)	
Total	67	67	134	

There was no difference in the medical complications in both the groups. In oral misoprostol group 10 women were on medical nutritional therapy for gestational diabetes mellitus and 14 women in oxytocin arm.

Methods of confirming leaking

Methods used to confirm leaking were similar in both the groups.

Table 5

	Oral Misoprostol	oxytocin	Total	
Obvious leaking	11(16.42%)	14 (20.90%)	25(18.66%)	
Speculum	53 (79.10)	44 (65.67%)	97 (88.99%)	p value 0.233
ACTIM PROM	1 (1.49%)	4 (5.97%)	5 (4.59%)	
Definite history	2(2.98%)	5 (7.46%)	7 (6.42%)	
total	67	67	134	

Hours of leaking before Randomization

In oral misoprostol group median for duration of leaking before randomization was 5and in oxytocin group it was 5.30 hours.

	Mean(S.D.)	Minimum	Maximum	Median	p value 0.6691
Oral Misoprostol	8.25(9.14)	0	48	5	
Oxytocin	6.48(5.01)	0.45	32.30	5.30	

Table 6: Hours of leaking before Randomization

PRIMARY OUTCOME:

1. Duration of induction to delivery

The mean duration of time interval between induction to delivery is 12.77±7.4h in misoprostol group and mean duration in oxytocin group are 11.73±5.52h. There was no significant difference in both the groups.

Table 7: Mean time interval between induction to delivery (in hours)

	Median	Minimum	maximum	Mean	p value
Oral misoprostol	10.49	1.54	29	12.77(7.14)	0.6774
oxytocin	11.32	2.13	25.02	11.73(5.52)	

2. Vaginal delivery within 24 hours

There were 77.61% vaginal deliveries within 24 hours in misoprostol group and 75.37% in oxytocin group. Total vaginal deliveries in misoprostol group were 58 and in oxytocin group were 50 showing greater incidence of vaginal deliveries in misoprostol group.

Table 7:

	Oral misoprostol (%)	Oxytocin (%)	Total (%)	p value
<24 hours	52 (77.61)	49(73.13%)	101(75.37%)	0.047
>24 hours	6(8.96)	1 (1.49)	7(5.22)	
LSCS	9(13.13)	17 (25.37%)	26(19.40)	
Total	67	67	134	

3. Caesarean section rates

Caesarean section rates in oral misoprostol and oxytocin were 13.13% and 25.37% with lesser incidence of caesarean delivery in misoprostol group.

Table 8: Incidence of caesarean delivery

	Misoprostol	Oxytocin	Total
No of LSCS	9	17	26
Percentage	13.13%	25.37%	19.40%

Indications of Caesarean sections

Table 8

Indications	Oral Misoprostol	oxytocin
Failed Induction	1	9
NRFS(non reassuring fetal status)	4	6
Protracted Dilatation	0	1
Arrest of dilatation	2	0
Arrest of descent	1	1
Breech in labour	1	0
Total	9	17

Measures of effectiveness

1. Total Duration of oxytocin infusion

The mean duration of oxytocin infusion in misoprostol group was 6.49h and in oxytocin group was 9.20 h which showed significant difference in both the groups.

Table 9

	Mean (S.D)	Minimum	Maximum	Median	P=0.002
Oral Misoprostol	6.49 (4.67)	0.19	22.30	5.18	
oxytocin	9.20 (5.03)	0.08	21.00	9.30	

2. Total Amount of oxytocin given

The amount of oxytocin required is significantly more in oxytocin group than in misoprostol group.

	Mean(S.D.)	Minimum	Maximum	Median	P – value 0.0002
Oral Misoprostol	2.70(2.88)	0.3U	10.50U	2	
Oxytocin	4.93(3.84)	0.10U	17.50U	4.50	

Table 10: The amount of oxytocin required

II. A. Complications (maternal)

Uterine hyperstimulation with CTG abnormalities

There was no significant difference in occurrence of uterine hyperstimulation with CTG abnormalities in both the groups.

Table 11: Occurrence of uterine hyperstimulation

	Oral Misoprostol	oxytocin	Total	P- value 0.381
Yes	8(11.94)	5(7.46)	13(9.70)	
No	59(88.06)	62(92.54)	121(90.30)	

Trace abnormalities requiring Terbutaline

Out of 8 women who had trace abnormalities in oxytocin group 7 required terbutaline and all 5 in oxytocin group were given terbutaline.

Table 12: Terbutaline requirements

	Oral Misoprostol	oxytocin	P >0.99
Yes	7(87.50)	5(100)	
No	1(12.50)	0(0)	

Postpartum haemorrhage

Postpartum haemorrhage in oxytocin group was 8.96% and in oxytocin group was 2.99% but there was no statistical significant difference.

Table 13

	Oral Misoprostol	oxytocin	Total	P=0.145
Yes	6(8.96%)	2(2.99%)	8(5.97%)	
No	61(91.04%)	65(97.01)	126(94.03%)	

Blood Loss in ml

Blood loss was observed to be less than 500ml in 88.06% in misoprostol group and 77.61% in the oxytocin group.

Table 14

	Oral Misoprostol (%)	Oxytocin (%)	P=0.145
<500ml	59(88.06)	52 (77.61)	
500-1000ml	7(1.45)	15(16.42)	
>2000ml	1(1.49)	0(0.75)	

Intrapartum Antibiotics

There were 3 women in misoprostol group and 2women in oxytocin group received antibiotics for chorioamnionitis.

Table 15: Use of intrapartum antibiotics

	Oral misoprostol	oxytocin	total	P-value
Prophylactic antibiotics	32 (47.76)	33(49.25)	65	0.898
Therapeutic antibiotics(chorioamnionitis)	3 (4.48)	2(2.99)	5	
No antibiotics	32(47.76)	32(47.76)	64	
Total	67	67	134	

Post-partum fever

There was no difference in occurrence of fever in both the groups

Table 16: Occurrence of fever

	Oral Misoprostol n=67	Oxytocin n==67	P>0.99
Yes	5(7.46)	5(7.46)	
No	62(92.54)	62(92.54)	

Post-partum fever with diagnosis of endometritis, UTI

Table 17: Incidence of post partum fever

There was 1 woman with endometritis in misoprostol group and 1 woman in oxytocin group.

	Oral Misoprostol n=67	Oxytocin n==67	
Endometritis	1(1.49)	1(1.49)	
UTI	1(1.49)	0(0)	
Others	4(5.97)	3(4.48)	
No	61(91.04)	63(94.03)	

B. Complications (Fetal)

CTG abnormality

There was 32.84% CTG abnormalities in misoprostol group 35.82% in oxytocin group. This showed greater incidence of CTG abnormalities in oxytocin group compared to misoprostol group. However there was no significant difference in both the groups.

Table 18: Incidence of CTG abnormalities

	Oral Misoprostol n=67	Oxytocin n=67	P=0.716
Yes	22(32.84%)	24(35.82%)	
NO	45(67.16)	43(64.18)	

Type of CTG abnormalities

Table 19: Type of CTG abnormalities

	Oral Misoprostol	Oxytocin group	P –value 0.113
CATEGORY I	5(22.73%)	3(12.50%)	
CATEGORY II	14(63.64%)	21(87.50%)	
CATEGORY III	3(13.64%)	0	
Total	22	24	

Most common type of abnormality seen was category II type non reassuring status in both groups with 63.64% in oral misoprostol group and 87.50% in oxytocin group. There were 3 women who had category III type trace in misoprostol group.There was no significant difference in both groups.

Description of CTG abnormalities

Table 20

	Oral Misoprostol	oxytocin
Early decelerations	2 (9.09%)	1(4.17%)
Variable decelerations	15(68.18%)	20(83.33%)
Severe variable decelerations	0	1 (4.17%)
Late decelerations	2(9.09)	1(4.17)
Complicated tachycardia	3(13.64)	1(4.17)

Still born

There were no still borns in both the groups.

Table 21

	Oral Misoprostol	oxytocin
Still born	0	0
Alive born	67(100%)	67 (100%)

C. Complications (Neonatal)

There was no significant difference in neonatal complications. 1 baby had a low APGAR(less than 7) after 5 minutes in oxytocin group. 1 baby in each of the groups had cord pH less than 7 .1.

Table 22: Incidence of neonatal complications

	Oral Misoprostol	Oxytocin
Neonatal sepsis	1 (1.49%)	0(0%)
Neonatal encephalopathy	0	0
Apgar <7 at 5min	0	1(1.49%)
Cord pH <7.1	1(1.49%)	1(1.49%)
Need for resuscitation	1(1.49%)	2(2.99%)

NICU (neonatal intensive care) admissions

There was no significant difference in the admissions of neonates in the intensive care unit.

Table 23

	Total	Oral Misoprostol	oxytocin	P=0.244
YES	7(5.22)	5(7.46)	2(2.99)	
NO	127(94.78)	62(92.54)	65(97.01)	

Indications for NICU admissions

There were 2 babies who were admitted in NICU for suspected sepsis in misoprostol group out which 1 had sepsis. There was 1 baby admitted for asphyxia in oxytocin group.

Table 24: Indications for NICU admissions

	Oral Misoprostol (%)	Oxytocin
Suspected Sepsis	2(2.98)	0(0.00)
Asphyxia	0(0.00)	1(1.49%)
Respiratory Distress	2(2.98)	0(0.00)
Hydronephrosis	1(1.49)	0(0.00)
Hypoplasticleft. aortic arch	0	1(1.49)
Total	5(7.46)	2(2.99)

III. Satisfaction

Care giver satisfaction (Score 1 -5)

Score more than 3 was 82.09% in oral misoprostol group and 71.64% in oxytocin group.

There was no significant difference in care giver satisfaction but greater incidence was seen in misoprostol group.

Table 25

Score	Total	Oral misoprostol	oxytocin	P=0.152
<=3	31(23.13)	12(17.91)	19(28.36)	
>3	103(76.87)	55(82.09)	48(71.64)	

Patient satisfaction (score 1 -5)

There was no significant difference in patient satisfaction scores. (Table 26)

	total	Oral misoprostol	oxytocin	P=0.602
4	59(44.03)	28(41.79)	31(46.27)	
5	75(55.97)	39(58.21)	36(53.73)	

Sub groups

1. Time interval between CTG abnormalities from the time of randomization

There was no significant difference in occurrence of CTG abnormality in both the groups from the time of randomization as shown in Table 27

	Mean(S.D.)	Minimum	Maximum	Median	P=0.8003
Oral Misoprostol	9.35(5.50)	0.20h	21.0h	8.85h	
Oxytocin	9.00(5.67)	0.20h	22.30h	9.15h	

2. Cervical effacement (1-5cm) at the time of CTG abnormality

Cervical effacement was not occurred completely in 3 women in misoprostol group and 5 women in oxytocin group at the time of CTG abnormality.

Table 28

	total	Minimum	Maximum	Median
Oral Misoprostol	3	1	2	2
oxytocin	5	1	5	3

3.Cervical dilatation at the time of CTG abnormality

Table 29

Dilatation(cm)	Oral Misoprostol	oxytocin	total	P=0.501
0	1(9.09%)	1(9.09%)	2(9.09%)	
1	1(9.09%)	2(18.18%)	3(13.64%)	
2	3(27.27%)	1	4 (18.18%)	
3	3(27.27%)	3(27.27%)	6(27.27%)	
4	0	2(1818%)	2(9.09%)	
5	0	1(9.09%)	1(4.55%)	
9	1(9.09%)	1(9.09%)	2(9.09%)	
10	2(18.18%)	0	2(9.09%)	

4. Station at the time of CTG abnormality

Table 30

Station	Oral misoprostol	oxytocin	total	P=0.156
-3	4(36.36%)	4(36.36%)	8(36.36%)	
-2	3(27.27%)	3(27.27%)	6(27.27%)	
-1	0	1(9.09%)	1(4.55%)	
0	0	3(27.27%)	3(13.64%)	
+1	3(27.27%)	0	3(13.64%)	
+2	1(9.09%)	0	1(4.55%)	
Total	11	11	22	

5. Postpartum fever with cultures positive:

Table 31

	Oral Misoprostol	oxytocin	Total
Urine culture	1(1.49)	2(2.99)	3(2.23)
Blood culture	1(1.49)	0	1(0.74%)

6. Number of doses of misoprostol given

Only 9(13.3%) women were given all three doses of misoprostol. 59.70% required only 1 dose of misoprostol.

Table 32

No of doses	No of women received	percentage
1	40	59.70 %
2	18	26.87%
3	9	13.43%
Total	67	100%

Reason for not giving all doses in nulliparous and multiparous

Contractions are the most common reason for not giving next dose of misoprostol.

Table 33

Reason	Oral Misoprostol
Contraction	50(96.17%)
Deceleration	1(1.92%)
Contraction &decelerations	1 (1.92%)
Total	52

DISCUSSION

The clinical management of premature mature of membranes is controversial. Options include expectant management versus active management. The results of Term PROM trial concluded that active management results lower risk of maternal morbidity and increased maternal satisfaction than expectant management(5) . ACOG guidelines 2016 recommends active management after premature rupture of membranes(48) . But there was no evidence to recommend appropriate method of induction of labour in women with pre labour rupture of membranes(52). WHO 2011 recommends traditional intravenous oxytocin for induction of labour for premature rupture of membranes(52).However induction with oxytocin needs continuous intravenous accesses and fetal monitoring and also restricts mobility even in early labour. Intra-vaginal prostaglandin E2 is other recommended method of choice which is less invasive requires less amount of oxytocin than traditional oxytocin alone(52). It is even approved by FDA for this purpose. But its cost and storage requirement makes its availability difficult especially for people in developing countries. Misoprostol an analogue of prostaglandin E1 shown not only to be effective in inducing labour but also cheaper, stable at room temperature(65). Misoprostol can be administered even orally which not possible with prostaglandin E2.

The purpose of this study was to determine safety and efficacy of oral misoprostol in a titrated regimen and compare it with traditional intravenous oxytocin for induction of labour in women with prelabour rupture of membranes at term.

The study of Ngai et al. found that the time interval from induction to delivery was significantly longer in oxytocin group than in misoprostol group(11.1±4.9h and 7.3±3.1h, respectively).They used 100mcg every 4 hours upto maximum of 3doses(3)

In the study of Al-Hussain et al the duration of induction to delivery was shorter in oral misoprostol group when compared with oxytocin group (5.5±2.9 and 10.8±4.8h respectively). But the occurrence of contractile abnormalities are more in misoprostol group(66).

In the present study we used 50mcg of oral misoprostol every 4 hourly to a maximum of 3 doses in nulligravida and a maximum of 2 doses in multiparous women to avoid contractile abnormalities. The study showed similar findings with the mean time interval between induction to delivery being 12.77±7.14 h in the oral misoprostol group and 11.73±5.52 h in the oxytocin group with a significant difference between two.

These results were similar to Peter C. Cheung et al who found significantly shortened delivery interval from PROM in 100mcg oral misoprostol group but not in 50mcg group when control (100mcg group14.5±6.2h , 50mcg group 13.0±6.1h, control 25.1±10.5h).But they concluded that it was as effective as 100mcg in achieving vaginal delivery(65)

Our result of mean time interval was not in agreement with the study of Crane et al who found significantly longer induction to delivery interval in oral misoprostol group (12.28 ± 7.1h) compared to oxytocin group (9.55±5.3h). Crane et al administered 75 mcg of misoprostol by breaking a 100mcg tablet. There was no upper limit for the

number of doses of misoprostol and the start of oxytocin for augmentation was not clearly known.

Ayman et al. showed induction to delivery interval was significantly shorter in misoprostol group compared to oxytocin group (6.59±1.91 and 9.30±2.58h). They used 100mcg every 4 hours maximum of 3 doses. The number of nulliparous in this study was 58% as compared to the present study which had 74.63% are nulliparous.

There were 9 women who underwent caesarean sections in misoprostol group and 17 in oxytocin group and there was no significant statistical difference between both the groups(P=0.047) but there was greater incidence of caesarean sections in oxytocin group 25.37% when compared to misoprostol group 13.13%.There were 58 women (86.56%) in the misoprostol group and 50 women (74.64%) in oxytocin group delivered vaginally.52 women (77.61%) in misoprostol group and 49 women (73.13%) in oxytocin group delivered within 24 hours. Although there was no significant difference in the number of vaginal deliveries between both the groups .There was greater incidence of vaginal deliveries in the misoprostol group.

These findings were similar to previous studies which showed no significant differences in the mode of delivery. For example, a study done by Butt et al (67) showed a caesarean section rate of 14% in oral misoprostol group and 13.3% in oxytocin group. Mozurkewich study showed 20.1% in oral misoprostol group and 19.9% in oxytocin group(68). Nagi et al showed 5% incidence of caesarean section in oral misoprostol group and 7.5% in oxytocin group.(69). Tayel et al showed 6% of caesarean sections in misoprostol group and 12% in oxytocin group with no significant difference in the mode of delivery(70).

In the present study women who has not entered active phase of labour after 18 hours of oxytocin are considered as failed induction in oxytocin group. There were 9(13.3%) caesarean sections for failed induction in oxytocin group and 1(1.49%) in oral misoprostol group. In oral misoprostol group failed induction was considered only after giving 12 hours of intravenous oxytocin for augmentation. These results were in agreement with Tayel et al study in which 4 cases (8%) had caesarean sections for failed progression in oxytocin group and non-occurrence of failed progression in oral misoprostol group(70).

A Study done by Tarik et al also found that all caesarean section done in oxytocin group were because of failed progression i.e. non-progression of labour(71). However Butt et al found failed progression is the most common indication for both the groups 10.9% in misoprostol group and 11.3% in oxytocin group. Emergency caesarean section for non-reassuring fetal status misoprostol group were 3 (4.47%)and 1(1.49%) for fetal distress. In oxytocin group there were (6 8.9%) caesarean sections for non-reassuring fetal status. There was no fetal distress in oxytocin group.

In misoprostol group of present study 59.70% required single dose of 50mcg oral misoprostol. These findings are similar to Ngai et al study in which60% of women required only single dose of misoprostol(3). These results were in agreement with Tayel et al study who found that 60% required only single dose of misoprostol rest 40% required more than one dose (70).

The mean duration of oxytocin given was 6.49±4.67h in misoprostol group and 9.20±5.03h in oxytocin group which showed significant difference (p=0.002).This allows ambulation in early labour in misoprostol group which is not possible in

oxytocin group.19(28.35%) women delivered without of oxytocin in misoprostol group and the rest 48(71.64%) women in misoprostol group received oxytocin for augmentation.

The mean amount of oxytocin required in misoprostol group was 2.7±2.88units and in oxytocin arm was 4.93±3.84 units which showed significant difference p=0.0002.

There were no significant difference in occurrence of tachysystole, and hyperstimulation in between both the groups. There were 8(11.94%) women in misoprostol group and 5(7.46%) women in oxytocin group with contractile abnormalities. These findings were in agreement with that of Mozurkewich , who found no significant difference in occurrence of contractile abnormalities in both the groups (10.7 % in misoprostol group and 8.8% in oxytocin group)(68). Tayel et al study also showed no significant difference in occurrence of hypertonus and hyperstimulation in both the groups(4% in misoprostol group and 2% in oxytocin group)(70). Similarly Crane et al found no significant difference in the occurrence of contractile abnormalities (42) (6% in misoprostol group and 4.1% in oxytocin group).

There were 3 cases of chorioamnionitis in misoprostol group and 2 case in oxytocin group without significant difference (4.48%vs. 2.55%; p=0.898).These findings are similar to many other studies that showed no significant difference((69).

No significant difference was found between the two groups in the occurrence of postpartum haemorrhage. 6 women in misoprostol group and 2 women in oxytocin group had postpartum haemorrhage (8.96% vs 2.99%; P= 0.145). These findings are similar to other studies. For example Tayel et al found one atonic postpartum haemorrhage in misoprostol group (2%) and 2 (4%) in oxytocin arm(70) out of 50

cases in each arm. Similar results occurred in the study done by Crane et al with 3.8% occurrence of postpartum haemorrhage in misoprostol group and no occurrence in oxytocin group(42).However in present study 88.06% of women in misoprostol had less than 500ml of blood loss and 77.61% in oxytocin less than in oxytocin group. Thus, greater number of women in misoprostol group had less blood loss.

Fetal Complications

There was 1 baby with Apgar score less than 7 at 5 minutes in oxytocin group. In the misoprostol group there were no babies with Apgar less than 7.These findings are similar to other studies. Crane et al showed (4% in misoprostol vs. 8% oxytocin group).

There was no significant difference in the neonatal outcome in both the groups. There was 1 baby in misoprostol group and 1 in oxytocin group with cord pH less than7.1. There was 1(1.49%) baby in misoprostol group required resuscitation and 2(2.99%) in oxytocin group required resuscitation. There was 1 baby with neonatal sepsis. There was no occurrence of sepsis in oxytocin group.

In our study 5 (5.52%) babies in the misoprostol group and 2 (2.99%) babies in oxytocin group were admitted in neonatal intensive care though there was no significant difference.

These findings are similar to Tayel et al 4(8%) cases in oxytocin group and 2(4%) cases in misoprostol group. Crane et al found 3.8% incidence in misoprostol group and 5.7% in oxytocin group. Even though there was no statistically significant difference in both groups there was a greater incidence in oxytocin group.

Occurrence of postpartum fever was similar in both the groups i.e. around 7.46%. 1 woman on oxytocin group and 1 woman in misoprostol group had endometritis.

There were no wound infections in either of the groups. There was no occurrence of still born in both the groups. There was no cord prolapse in both the groups.

CONCLUSIONS

From the above analysis the researches of this study conclude that

- Oral misoprostol is the preferred method as compared to traditional intravenous oxytocin for induction of labour as it does not need intravenous access which restricts ambulation in early labour.
- There is a clinically significant difference between the two arms of this study in regards to the lower incidence of caesarean sections in the oral misoprostol group without any difference in induction to delivery interval.
- The neonatal and maternal morbidity outcomes were not different in both study arms.
- As recommended by other studies, dose adjustments in this study showed a similar low occurrence of contractile abnormalities in both study arms. This goes to show that oral misoprostol would be a preferred treatment modality in all situations requiring intravenous oxytocin for induction of labour in premature rupture of membranes.

LIMITATIONS

- This was not a placebo controlled trial and therefore the efficacy and the effectiveness of oral misoprostol as a single best agent in term prelabour rupture of membranes cannot be commented upon.
- The study sample size was limited to a permuted small block randomisation of the patients which though advantageous that both the blocks are equal in size with uniformly distributed by key outcome characteristics, it increased the chance that this randomisation or allocation process may be predictable, especially in this study since the randomisation is open (it is obvious whether the patient is receiving intravenous oxytocin) and there is a chance that the randomisation can be unmasked.
- Randomisation also did not guarantee comparable groups as differences in confounding variables could arise.
- Complications that occur infrequently could not be studied due to the small sample size.
- A larger sample size would show a statistically significant difference rather than just a clinical difference in the incidence of caesarean sections.

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ANNEXURES

ANNEXURE I – INSTITUTIONAL REVIEW BOARD CLEARANCE

ANNEXURE II -PATIENT INFORMATION SHEET AND CONSENT FORMS

ANNEXURE III – PROFORMA

ANNEXURE IV – MASTER SHEET

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Ethics Committee Registration No: ECR/326/INST/TN/2013 issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. of India

Dr. George Thomas, D Ortho Ph.D.
Chairperson, Ethics Committee

Dr. B. Antonisamy, M.Sc., Ph.D., FSMS, FRSS.
Secretary, Research Committee

Prof. Keith Gomez, B.Sc., MA (S.W), M.Phil.
Deputy Chairperson, Ethics Committee

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho.
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD, MNAMS, DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

December 08, 2015

Dr.Shiny Nirupama Boddu
PG Registrar,
OG - 5,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Funding: New Proposal**
A non-inferiority randomized trial comparing safety and efficacy of oral misoprostol with intravenous oxytocin for induction in prelabour rupture of membranes at term.
Dr.Shiny Nirupama Boddu (Employment Number: 52118, Obstetrics and Gynaecology), Dr.Jiji Mathews and Dr.Swati Rathore, Dr. Santosh Benjamin, Dr. Anuja Abraham, **Dr.** Antonisamy, Biostatistics

Ref: IRB Min No: 9710 [INTERVEN] dated 28.10.2015

Dear Dr.Shiny Nirupama Boddu,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "A non-inferiority randomized trial comparing safety and efficacy of oral misoprostol with intravenous oxytocin for induction in prelabour rupture of membranes at term" on October 28th 2015.

The Committee reviewed the following documents:

1. IRB Application format
2. Information Sheet and Informed Consent Form (English, Tamil, Hindi, Bengali)
3. Informed Consent Form (English, Tamil, Hindi,)
4. Proforma
5. Cvs of Drs. Shiny Nirupama Boddu, Jiji Mathews, Swati Rathore, Antonisamy, Santosh Benjamin, Anuja Abraham
6. No.of documents 1-4
7. Self care Management Support
8. No.of documents 1- 11

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

Dr. George Thomas, D Ortho Ph.D.
Chairperson, Ethics Committee

Dr. B. Antonisamy, M.Sc., Ph.D., FSMS, FRSS.
Secretary, Research Committee

Prof. Keith Gomez, B.Sc., MA (S.W), M.Phil.
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Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

The following Institutional Review Board (Silver, Research & Ethics Committee) members were present at the meeting held on October 28th 2015 in the CREST/SACN Conference Room,Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Affiliation
Dr. George Thomas	MBBS, D Ortho, PhD	Orthopaedic Surgeon, St. Isabella Hospital, Chennai, Chairperson, Ethics Committee, IRB, Chennai	External, Clinician
Dr. B. Antonisamy	MSc, PhD, FSMS, FRSS	Professor, Biostatistics, Secretary (Research Committee), IRB, CMC, Vellore	Internal, Statistician
Dr. Prasanna Samuel	MSc, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Asha Mary Abraham	MBBS, MD, PhD	Professor, Virology, CMC, Vellore	Internal, Clinician
Dr. Anuradha Bose	MBBS, DCH, MD,MRCP, FRCPCH	Professor, Child Health, CMC, Vellore	Internal, Clinician
Dr. B. Poonkuzhali	MSC, PhD	Professor, Haematology, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Suresh Devasahayam	BE, MS, PhD	Professor of Bio Engineering, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Thambu David	MBBS, MD, DNB	Professor, Medicine, CMC, Vellore	Internal, Clinician
Dr. D. J. Christopher	BSc, MBBS, DTCD DNB, FRCP(Glasg), FCCP(USA)	Professor, Pulmonary Medicine, Associate Director (HR), CMC, Vellore	Internal, Clinician
Dr. Sathya Subramani	MD, PhD	Professor, Physiology, CMC, Vellore	Internal, Clinician

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

Prof. Keith Gomez	BSc, MA (S.W), M. Phil (Psychiatry Social Work)	Student counselor, Loyola College, Chennai, Deputy Chairperson, Ethics Committee, IRB	External, Lay Person & Social Scientist
Dr. P. Zachariah	MBBS, PhD	Retired Professor, Vellore	External, Clinician
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMC, Vellore	Internal, Legal Expert
Dr. Jayaprakash Muliyil	BSC, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, CMC, Vellore	External, Scientist &Epidemiologist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Vinitha Ravindran	PhD (Nursing)	Professor & Addl. Deputy Dean, College of Nursing, CMC, Vellore	Internal, Nurse
Dr. Binu Susan Mathew	MBBS, MD	Associate Professor, Clinical PharmacologyCMC, Vellore	Internal, Pharmacologist
Mrs. Ruma Nayak	M Sc (Nursing)	Professor, Head of Paediatric Nursing & Deputy Nursing Superintendent, College of Nursing, CMC, Vellore	Internal, Nurse
Dr. Shirley David	MSc, PhD	Professor, Head of Fundamentals Nursing Department, College of Nursing, CMC, Vellore	Internal, Nurse

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Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

We approve the project to be conducted as presented.

The institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent.** On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link:

http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "A non-inferiority randomized trial comparing safety and efficacy of oral misoprostol with intravenous oxytocin for induction in prelabour rupture of membranes at term" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in)

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board
Christian Medical College, Vellore

Dr. NIHAL THOMAS
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin), FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min No: 9710 [INTERVEN] dated 28.10.2015 4 of 4

Informed Consent form to participate in a research study

Study Title: A randomized controlled trial comparing safety and efficacy of oral misoprostol versus intravenous oxytocin for induction in pre-labour rupture of membranes at term.

Study Number:

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age:_____

Please initial box

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____

PATIENT INFORMATION SHEET

A randomized controlled trial comparing safety and efficacy of oral misoprostol with intravenous oxytocin for induction in pre-labour rupture of membranes at term

This is a study for women admitted in the Labour Room with bag of waters that are broken before the onset of labour pains after 37 weeks.

Delivery after long duration of leaking is associated with fear, apprehension and inconvenience to the pregnant lady, family members and the caregiver.

It has long been known by obstetricians that prolonged duration of rupture of membrane increases the risk of maternal and neonatal infection. The intravenous injection is the standard of care. Unfortunately, this form of care prevents the woman from being ambulant. The oral drug called misoprostol has been shown to be as effective in some studies. This drug and dosage is already being used in pregnant women for induction of labour without rupture of membranes. We currently do not know for sure the ideal mode of management in women whose bag of waters are broken before the onset of labour pains.

We would like to invite you to be part of this research study. If you are willing to participate in the study, you may be randomly assigned either to the injectable group or the oral misoprostol group.

Both these drugs are routinely used in our hospital.

If you are assigned to oral misoprostol group you will receive a tablet which has to be taken orally and it will be given once in four hours maximum of 3 doses. Before each scheduled dose you will assessed whether you are in labour or not. You will be given the drug only if you are not in labour. If you are still not in labour after 3 doses we will follow our routine labour room protocol for further management.

The information regarding the duration of labour, occurrence of fever, baby's heart rate patterns, antibiotic usage, etc. will be collected.

There will be no benefits or increased risk by being part of this study. However, for some reason if you do not choose to be part of this study you will have no disadvantage. You always have the option of withdrawing from the study without your medical care being affected.

Proforma

Oral Misoprostol

**only for misoprostol*

1.Serial number/Unique ID(slno)

2. Randomization of group(ramdomgro) 1.Oral misoprostol

3. Name of the patient(name) _____

4.Hospital Number(hosno)

5. Date of Randomization(dor)

6. Age in years(age)

7.Gestational age in weeks & days(gestationa)

8.Parity (parity) 1. 0

9.Height in cms(height)

10.Weight in kgs(weight)

11. BMI(bmi)

12. Obstetrics Medical complications(omc) 1. GDM on diet
3. Epilepsy

13. Obvious leaking (obvious) 1. Yes

14. If No, confirmed by (ifno) 1. Speculum exam
4.Definite history of leaki

14a. Time of randomization(am/pm) (timerando)

15. No of hours leaking before randomization(timerando 1)

16.No of hours from leaking to delivery (Q15+Q20=Q16) (leakrandon)

If q16>24 hours ,then culture and neonatal antibiotics mandatory)

18. Time of 1st PV (hours after randomization)	(n1st PV)
*19. Reason for 1 st pv is done before 12 hrs in prmi	1. Contraction
& 8 hrs in multi(reasonpv)	3. Fever
	5. Contraction &decelara
20. Total Duration from randomization to delivery in hrs & mts	(duration)
21. Mode of delivery(deliverymo)	1. Normal
22.If LSCS indication for the same (iflscs)	
1. Failed induction	2. Fetal distress
5. Arrest of dilatation	7.Others(specify)- (lscsot
23. Vaginal delivery occurred within 24 hours of delivery (vaginal)	1.Yes
*24. No of doses of Misoprostol(misoprosto)	1. 1
25.No of PVs (totalpv)	
*26.Protocol Deviation(protocol)	1. yes
*27.Reason for not giving all three	1.Contraction
3 doses in primi and 2 doses in multi (doses)	3.Fever
	5.Contractions and decel
* 28 .Oxytocin used in misoprostol group(oxytocin)	1.yes
(Always refer nurses record)	
*29.Time of starting Oxytocin (duration after randomization) (*Always refer nurses record*)	(startoxyto)
30*Total Duration of Oxytocin(duroxyto)	
*31. Was the oxytocin started before total doses of misoprostol for inadequate contractions?(wasoxyto)	1.yes
32.Total units of oxytocin used(totalunit)	Units 2.5, 5, 7.5
1st pint	

2nd pint

3rd pint

4th pint

(Always refer nurses record)

33.CTG abnormality (*if no skip Q34 to 41)(ctg)* 1.yes

34. If yes (ctgyes) 1.Category I

35.Description of decelaration (decelarati) 1.Early decelaration
4.Severe Variable decelaration

36. Time in hours of CTG abnormality from randomization (ctgrandom)

37. Cervical dilatation@CTG abnormality(cms) (cervical)

38.Effacement @ CTG abnormality(cm) (effacement)

39.Station @ CTG abnormality(stationctg)

40. Amnioinfusion(amnion) 1. Yes

41.Tachysystole(tachsystol) 1. Yes

42.Trace Abnormalities(trace) 1.Yes

43.Requiring Terbutaline(traceyes) 1.Yes

44. Liquor colour(color) 1.clear

45.If MASF (ifmsaf) 1.Thick

46. If MSAF after randomization ,then time from randomization (msafrando)

47.Cord prolapse(cord) 1.yes

48.Blood Loss(bloodloss)	1. <500ml 4. 1500-2000
49.PPH (pph)	1.yes
50. Cause of PPH (causepph)	1.Atonic
51. Intrapartum Antibiotics(intrapartu)	1. Yes
52. If yes ,details (intrayes)	1.Prophylactic
53.If 2 (ifintrayes)	1.Chrioamnionitis 3.Intrapartum fever
54.Post partum fever (ppfever)	1.yes
55. Postpartum antibiotics (ppanti)	1.yes
56. If yes (ppantiyes)	1.UTI 3.Wound Infection
57.diagnosis of Endometritis (diagendo)	1.Clinical
58.Culture +details (culturedet)	1. Urine
59.If yes (details, organism Etc) (if yes)	
60.Outcome of the baby (outcome)	1.Alive
61.Need for resusitation (nfr)	1. Yes
62. Apgar <7 at 5 minutes (apgar)	1.yes
63.Cord pH less than 7.2(cordph)	1.Yes
64.Neonatal Encephalopathy (neonatal)	1.yes

(Seizures, HIE, etc)

65.Admission to NICU (nicu)	1. Yes
66. If yes, Indication (nicuyes)	1.sepsis
67.Neonatal Sepsis(neosepsis)	1.Yes
68.Is the baby Cultured (babycul)	1.yes
69.If yes ,give details (neosepyes)	1.CRP

70.Duration of Antibiotics(baby) (duranti)

71.Patient satisfaction Score(1-5) (satisfacti)

72. Care giver satisfaction Score(1-5) (care score)